DEPARTMENT OF HEALTH AND HUMAN SERVICES
Office of Therapeutics Research and Review
Center for Biologics Evaluation and Research
Food and Drug Administration

MEMORANDUM

DATE: October 22, 1999

FROM: Barbara G. Matthews, MD, MPH
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SUBJECT: Review of BLA submission 99-O 128
Infliximab (REMICADE) for signs and symptoms of rheumatoid arthritis

THROUGH: Karen Weiss, MD
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TO: File

1.0 Introduction

1.1 Proposed indication.

Infliximab is licensed as a single dose for the acute treatment of Crohn's disease and for 3 doses to close enterocutaneous fistulae in patients with fistulizing Crohn's disease. This supplement to the license application is to extend the indication to patients with rheumatoid arthritis. The proposed amended indication pertaining to rheumatoid arthritis is:

New Indication

Rheumatoid Arthritis
1. for the reduction of signs and symptoms in rheumatoid *arthritis* patients who have an inadequate response to methotrexate.

1.2 Dose

Based upon their review of the 30-week clinical data generated in the pivotal trial, C0168T22 (T22, ATTRACT), the sponsor proposed originally to license the dose of 3 mg/kg every 8 weeks administered intravenously. During the review of the clinical data, the sponsor analyzed the response of patients treated with infliximab through week 54 and found that more patients treated with infliximab at the dosing regimen, 10 mg/kg every 8 or 4 weeks, continued to respond in the assessment of signs and symptoms. The clinical response in patients treated with infliximab at all dosing regimens through week-54, including the 3 mg/kg given every 8 weeks, was statistically greater compared to the number of patients who responded to placebo in addition to methotrexate. Because of the suggestion of increased durability of response through week 54, the sponsor amended the proposed dosing to:

"An initial 3 mg/kg intravenous infusion over a 2-hour period is to be followed with additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Remade should be given in combination with methotrexate."

1.3 Organization of this Review

In addition to the supplement to the license submitted by the sponsor in January, 1999, this review incorporates the additional safety update through week 54 submitted by the sponsor in April, 1999 and further analyses of infections and human antichimeric antibody formation (HACA) submitted in July, 1999. The review is organized into 4 sections:

- Background
- Review of the safety and efficacy data from the pivotal clinical trial, T22 (ATTRACT)
- Review of the safety and efficacy data from the supportive clinical trial, T14
- Review of the Consolidated Safety Database including the review of data detailing the occurrence of delayed hypersensitivity reactions (BLA 99-0102)

2.0 Background

2.1 Overview of Rheumatoid Arthritis

First described as a clinical entity in 1 SOO, rheumatoid arthritis (RA) is a chronic multisystemic inflammatory disease with prominent autoimmune features. Although the principal characteristic of rheumatoid arthritis is persistent inflammatory synovitis, it displays a variety of clinical manifestations as defmed by the American College of Rheumatology:

- Morning stiffness (≥ 1 hr)
- Swelling of joints (≥ 3)
- Swelling of soft tissue of hand joints (PIP[a], MCP[a], wrist)
- Symmetrical soft tissue swelling
- Subcutaneous nodules
- Serum rheumatoid factor
- Radiographic evidence of erosion or periarticular osteopenia in hand or wrist joints

[a] PIP = proximal interphalangeal; MCP = metacarpophalangeal
Criteria 1 to 4 must be continuous for 6 weeks. A diagnosis of rheumatoid arthritis requires that 4 of the 7 criteria be fulfilled.

The potential for synovial inflammation to cause pain, swelling, and tenderness, with subsequent cartilage destruction, bone erosion, and joint deformities, is a cardinal manifestation of rheumatoid arthritis. Joint involvement is typically symmetrical, a characteristic usually not found in other forms of arthritis. Systemic, extra-articular symptomatology can include, fatigue, fever, weight loss, anemia, rheumatoid nodules, rheumatoid vasculitis, pleuropulmonary manifestations (e.g., pleural disease, interstitial fibrosis), pericardial effusion, Felty's syndrome (rheumatoid arthritis accompanied by splenomegaly, neutropenia, leg ulcers, thrombocytopenia, and the HLA-DR4 haplotype), keratoconjunctivitis, and osteoporosis.

The clinical course of rheumatoid arthritis can vary considerably. Some patients may experience only mild oligoarticular illness of short duration with minimal joint involvement, while others will experience polyarthritis, accompanied by marked joint deformities. For most patients, however, rheumatoid arthritis follows an intermediate course.

Epidemiology. The onset of rheumatoid arthritis is most frequent during the fourth and fifth decades of life, with 80% of all patients developing the disease between the ages of 35 and 50 years. The overall prevalence of rheumatoid arthritis is about 1% (range 0.3% to 2.1%), with women affected three times more often than men. The increased risk for RA among women remains unexplained, but suggests a hormonal basis as one factor in rheumatoid arthritis development. Evidence supporting this hypothesis includes the observed protective effect seen with the use of oral contraceptives, and the increased susceptibility for rheumatoid arthritis in women who never bore children and among women during the first 3 months postpartum. The gender difference in the incidence of rheumatoid arthritis tends to diminish with age, however.

Rheumatoid arthritis is associated not only with disability and pain but with increased mortality as well. The median life expectancy for patients with rheumatoid arthritis is shortened by 3 to 7 years, although increased mortality seems to be limited to patients with severe rheumatoid arthritis and has been attributed largely to infection andgastrointestinal bleeding.

Etiology. Despite intensive research, the cause of rheumatoid arthritis remains unknown. The pathogenesis of this disease is likely multifactorial and research has implicated 3 interrelated processes: genetic factors, microbial infections, and autoimmune reactions.

Family studies reveal that rheumatoid arthritis has a genetic component. Severe rheumatoid arthritis is found at 4 times the expected rate in first-degree relatives of patients with rheumatoid arthritis, and about 10% of the patients with rheumatoid arthritis have an affected fast-degree relative. Additionally, monozygotic twins are at least 4 times more likely to be concordant for rheumatoid arthritis than dizygotic twins.

The role of genetic influences in the development of rheumatoid arthritis is further highlighted by the association of this disease with the class II major histocompatability complex (MHC) gene product of the human leukocyte antigen (HLA)-DR series. Up to 70% of the patients with rheumatoid arthritis'express HLA-DR4 compared with 28% of control individuals, with HLA-DR1 found in a majority of HLA-DR4-negative patients. HLA is an important genetic factor in rheumatoid arthritis, and the risk for this disease is thought to be associated with a sequence of amino acids within the third hypervariable region of certain DRB1 alleles. It is now clear that HLA is not directly associated with the onset of synovitis, but, rather, is associated with the progression and severity of the disease process. The HLA-DRB1*0401/0404 genotype is particularly associated with severe, erosive, and seropositive rheumatoid arthritis.

HLA genes contribute only a portion of the genetic susceptibility to rheumatoid arthritis; other genes, such as those controlling the expression of T-cells and both the immunoglobulin heavy and light chains, may also be involved, as well as environmental factors.

An etiological link between certain microbial infections and the genesis of rheumatoid arthritis is supported by the fmdings that viral infections, such as rubella, Ross River virus, and parvovirus B19, are associated with the development of acute polyarthritis; and bowel infection secondary to Sahnonella, Shigella, and Yersinia infection can provoke joint inflammation. Moreover, in Crohn's disease and ulcerative colitis, bowel wall inflammation is complicated by joint inflammation in about 20% of the patients.

There is much information to demonstrate that rheumatoid arthritis is an autoimmune disease. Rheumatoid factors (RFs), or autoantibodies to the Fc portion of immunoglobulin G (IgG) molecules, are produced by B lymphocytes in the blood and synovial tissue of 80% of the patients with rheumatoid arthritis. These cases are termed "seropositive." High titers of serum RF are associated with more severe joint disease and with extra-articular manifestations, especially subcutaneous nodules. Despite the strong association between RFs and rheumatoid arthritis, RFs clearly do not cause the disease, since RF elevations also occur with other diseases, such as tuberculosis and cirrhosis.

Although a variety of cells are important in perpetuating the chronic damage seen in rheumatoid arthritis, the actions of macrophages may be of particular importance. Once in the synovium, macrophages are capable of antigen presentation and T-cell activation. Moreover, the degree of synovial macrophage infiltration correlates with rheumatoid arthritis severity and progression. HLA-DR4 and HLA-DR1 activate CD4+ lymphocytes, which then produce lymphokmes, including interferon and IL-2 that stimulate macrophages to produce IL-1 and TNFα. These macrophage-derived cytokines appear to be strongly involved in the induction and perpetuation of the chronic inflammatory processes of the joints seen in rheumatoid arthritis as well as the systemic manifestations of this disease.

Although the precise mechanism by which bone and cartilage destruction occur in rheumatoid arthritis is not completely understood, the cytokines IL-1 and TNFα play an important role by stimulating cells in the inflamed synovium to produce proteolytic enzymes, including collagenase and stromelysin, that can degrade tissue. The systemic manifestations of rheumatoid arthritis, such as malaise and fatigue, may result from the release of inflammatory cytokines from the synovium. The maintenance and propagation of RA appear to be immunologically mediated inflammatory processes, although the initial cause of this disease remains unknown. Thus, pharmacologic agents that block key steps in the inflammatory process might be expected to provide symptomatic relief and to slow disease progression.

Current Treatments in rheumatoid arthritis. The principal goals in the treatment of rheumatoid arthritis are to relieve pain, preserve or improve functional capacity, reduce inflammation, and prevent structural damage. Since the etiology of RA is unknown and its pathogenesis is speculative, treatment is typically empirical. The pharmacologic management of RA usually involves two approaches: symptom control and disease modification.

Simple analgesics, such as acetaminophen, NSAIDs (e.g., aspirin, indomethecin, ibuprofen, and naproxen), and, if necessary, low-dose corticosteroids (such as prednisone), have been used as first-line therapy to control the symptoms of rheumatoid arthritis. They exert minimal effects on disease progression, however. With the long-term and high-dose therapy often required to treat the pain associated with rheumatoid arthritis, NSAID use can cause a wide spectrum of toxic effects, including gastric irritation, platelet dysfunction, and liver function abnormalities.

NSAIDs act by blocking cyclooxygenase, and thus, the production of prostaglandins and other mediators of pain and inflammation. Cyclooxygenase, however, exists as 2 isoforms: COX-1, involved in normal physiologic functioning and gastroprotection, and COX-2, induced by inflammatory mediators. Typically, NSAIDs nonselectively inhibit both COX isoforms, increasing their side-effect liability. However, selective COX-2 inhibitors like meloxicam appear comparable in efficacy to standard NSAIDs in the treatment of rheumatoid arthritis, but with an improved gastrointestinal tolerability profile.

Of the available anti-inflammatory drugs, only corticosteroids are known to interfere with the synthesis and actions of cytokines. Although corticosteroids exert both anti-inflammatory and immunosuppressive effects, their serious potential for side effects, such as osteoporosis, muscle weakness, glucose intolerance, and cataracts, limits these agents to short-term use.

Current first-line therapy utilizes a variety of agents classified as disease-modifying anti-rheumatic drugs (DMARDs), even though there is little evidence they actually ameliorate the underlying disease process. These agents include gold, sulfasalazine, hydroxychloroquine, D-penicillamine, and irnmunosuppressants like azathioprine and methotrexate. Although the majority of patients seem to improve on DMARD therapy, benefits can be delayed for weeks or months; therefore, these agents are also known as slow acting antirheumatic drugs. In addition, these agents are associated with considerable toxicity, requiring careful patient monitoring. For example, azathioprine may cause blood dyscrasias (thrombocytopenia and leukopenia) or gastrointestinal discomfort.

Recently, the use of methotrexate (MTX), a cytotoxic immunosuppressant and anti-inflammatory agent, has increased significantly in the treatment of rheumatoid arthritis. In a study that included patients with long-term, progressive rheumatoid arthritis, MTX was shown to produce clinical improvements, including a decrease in the number of swollen joints and pain, and an increase in grip strength and mobility. In this study, however, 83% of patients experienced at least one adverse event, and 16.5% withdrew because of side effects. Indeed, toxicity is a serious concern with the use of MTX; which can induce stomatitis, thrombocytopenia, bone marrow suppression, puhnonary lesion, and hepatic fibrosis.

TNFα plays a key role in the pathogenesis of RA. This cytosine is overproduced in rheumatoid arthritis joints and triggers increases in synoviocyte proliferation and a cascade of secondary mediators involved in the recruitment of inflammatory cells and in the process of joint destruction. These findings make TNFα a logical target in the treatment of rheumatoid arthritis.

In transgenic mouse experiments, mice genetically engineered to produce large amounts of TNFα developed destructive arthritis, suggesting that this cytosine plays some role in the development of R4. When the mice were administered a monoclonal antibody against TNFα, *the* arthritis was completely abolished. In another animal model, the presence of intra-articular TNFα was shown to accelerate collagen-induced arthritis, contributing to more severe symptoms. Again, monoclonal antibodies to TNFα attenuated RA symptomatology.

2.2 Overview of Infliximab and Tumor Necrosis Factor (TNF)

Infliximab (cA2) is an anti-tumor necrosis factor α (anti- TNFα) antibody developed as a therapeutic agent for diseases in which TNFα is thought to mediate chronic inflammation. This antibody is a recombinant IgG 1, κ human-murine chirneric monoclonal antibody that specifically and potently binds and neutralizes the soluble TNFα homotrimer and its membrane-bound precursor.

TNFα is considered a key inflammatory mediator that exhibits a wide variety of functional activities. Overproduction of TNFα may lead to the disease processes associated with inflammation. High-affmity binding of infliximab to TNFα may inhibit or prevent the interactions of TNFα with its cellular receptors, thus preventing the deleterious effects caused by TNFα overproduction.

TNFα, as a trimer, can bind as many as three TNF receptors, and this cross-linking of receptors initiates signal transduction within the target cell. Two receptors for TNFα have been characterized: TNF-R p55 (TNF-RI) and TNF-R p75 (TNF-RII). These receptors are found on a wide variety of tissue and cell types. Binding of TNFα to TNF-R p55 induces cytotoxicity, fibroblast proliferation, synthesis of prostaglandins, up regulation of adhesion molecules, NF-κB activation, etc. The role of TNF-R p75 is less well defined; it appears to concentrate soluble TNFα at the cell surface for transfer to TNF-R p55 and may preferentially bind the transmembrane form of TNF for signaling. The inhibition of TNFα biological function by infliximab presumably occurs as a result of its ability to block the interaction of TNFα with its cellular receptors, suggesting that infliximab can inhibit TN&mediated signaling through either receptor *in vivo*. When infliximab is added to preformed TNF/TNF-R p55 or TNF/TNF-R75 complexes, a rapid (within 5 minutes) dissociation of TNFα from receptor is observed, with binding of dissociated TNFα to infliximab preventing reassociation with receptor.

Results obtained from the preclinical studies in transgenic murine models indicated that infliximab effectively and potently binds TNFα, that infliximab blocks the typical disease progression seen in RA, and that further study of infliximab in humans was warranted.

Six clinical trials were performed with infliximab in patients with rheumatoid arthritis. Single and multiple weight-adjusted intravenous infusions at doses of 1 to 20 mg/kg in the presence and absence of methotrexate were investigated in these infliximab clinical studies. A total of 660 patients with active rheumatoid arthritis participated in these 6 clinical trials of infliximab; of these patients, 553 were assigned to receive (and 555 actually received) treatment with infliximab.

The studies included 1 Phase I clinical trial (C0168T07); 1 open-label phase II clinical trial (C0168T18); 3 blinded, placebo-controlled phase II clinical studies (C0168T09, C0168T14, C0168T15/T17) and a randomized, double-blind, placebo-controlled Phase III trial (CO 168T22).

The initial trials of infliximab in patients with active, long-standing, erosive rheumatoid arthritis who had failed DMARD therapy, were designed to address issues important for selecting the appropriate dose and dosing interval. In the first trial, C0168T07, infliximab therapy at repeated doses of 5 and 10 mg/kg was shown to be effective in reducing the signs and symptoms of RA through the last follow-up evaluation 8 weeks after the last infusion. In CO 168T09, a single dose of infliximab at 1 mg/kg was shown to produce a clinical benefit, but that this benefit was less than the clinical benefit observed at single doses of 3 or 10 mg/kg. In C0168T15/T17, patients with an inadequate response to 10 mg/wk of MTX responded equally well to single infliximab doses of 5, 10, or 20 mg/kg. Especially notable was that patients receiving repeated infusions of 10 mg/kg had sustained clinical benefits at intervals as long as 8 weeks between infusions.

The pivotal clinical trial, C01 68T22 (T22, ATTRACT) and the supportive phase 2 clinical trial, C0168T14, are the focus of this review.

3.0 Review of the Safety and Efficacy Data from the Clinical Trial, C0168T22 (T22 or Attract).

3.1 Background

T22 is an ongoing placebo-controlled, double-blind, randomized study of chronic treatment of rheumatoid arthritis with infliximab. The trial has two endpoints. The first clinical endpoint was after all patients had completed 30 weeks and were assessed for a clinical response in their signs and symptoms: The clinical trial was initially planned to end after all patients had completed 54 weeks and their disease assessed for differences in radiological progression. However, the protocol was amended to extend the trial for two years with an interim analysis of the 54 week data. The 30 week endpoint of T22 represents the pivotal support for the proposed changes in indication. This review is of the 30 week data; the study period is March 31, 1997 to August 31, 1998.

Protocol Amendments. There were four amendments to T22.

Amendment 1 was dated April 29, 1997 and included the following revisions:

- Normalization of the CRP replaced normalization of the ESR in the criteria for clinical remission. The rationale for this change was to avoid the potential unmasking of the principal investigators by knowledge of the ESR changes. The CRP was assayed at a central laboratory whereas the ESR was assayed on site.
- Specified that the duration of infusion should not be less than 2 hours.
- Increased the number of sites from 25 to 35.

Amendment 2 was dated September 18, 1997 and included the following revisions:

- Increased the total number of patients to be randomized from -300 to -400 patients. The rationale was increase the number of patients in the safety database.
- Inserted the requirement for measurement of the ESR as a response variable at the week 30 and 54 evaluation visit. The rationale for this change was that ESR is a commonly monitored response variable in rheumatoid arthritis. Results of the ESR were unknown to the principal investigators until after the database has been locked for each endpoints.
- No longer excluded patients with history of squamous or basal cell carcinoma of the skin that had been treated with no evidence of recurrence.
- Amendment 2a dated September 18, 1997 applied only to clinical sites in France where the placebo formulation containing human serum albumin USP was replaced with 0.9% sodium chloride in order to comply with France's regulations.

Amendment 3 was dated August 29, 1998 and included the following revisions:

- Specified that in the primary analysis, epidural corticosteroids administration will be considered a treatment failure.
- Replaced the week 74 major visit with a week 78 evaluation visit, at which all patients will have an evaluation of all efficacy and safety parameters.
- Inserted the requirement for measurement of ESR as a response variable at week 78 and 98 visit.
- Specified that for the period in between the week 78 and 98 visits not all adverse events were to be assessed, but only serious infections, newly diagnosed malignancies and autoimmune diseases.

Amendment 4 was dated September 30, 1998 and included the following:

- Permitted patients to receive additional treatment during the second year (through 102 weeks) beyond the 54 weeks of treatment. The rationale was to comply with the guidance to industry document for a minimum of 1 year data to support the claim for improvement in physical function/disability and to comply with the European guidance for support of a claim for prevention of structural damage.

- Specified the follow-up schedule and procedures for patients participating in the second year treatment extension.

- Replaced the final week 98 major visit with a week 102 evaluation visit, at which all patients will have an evaluation of efficacy and safety parameters.

3.2 Clinical Study Design – T22 (ATTRACT)

T22 was a placebo-controlled, double blind, dose-ranging, randomized study of chronic treatment for patients with rheumatoid arthritis who continued to experience signs and symptoms while receiving methotrexate (MTX).

3.2.1 Objectives

The objectives of this trial were to evaluate the efficacy and safety of chronic treatment with infliximab in combination with methotrexate (MTX) in patients with active rheumatoid arthritis despite treatment with MTX. The primary objective was to determine the efficacy and safety of infliximab treatment in reducing clinical signs and symptoms of rheumatoid arthritis at 30 weeks following the onset of treatment.

Additional protocol-specified objectives of the study were to determine the efficacy and safety of infliximab treatment in providing continued reduction in signs and symptoms, reducing disability, retarding joint damage, providing disease remission, and improving quality of life at 1 and 2 years following the onset of treatment. The results of these later analyses will be provided after the appropriate timepoints.

3.2.2 Dose and dose-regimens

428 patients were enrolled. Four infliximab treatment groups were compared with placebo (MTX alone). Patients in each treatment group continued concurrent MTX treatment at the same dose as that received before the study (≥ 12.5 mg/wk orally or parentally). The dosing groups and treatment schedules are shown in Table 3.1.

Table 3.1 Treatment schedule through week 30 for the five dosing groups

Week	0	2	6	10	14	18	22	26	30
Infusion	1	2	3	4	5	6	7	8	Follow-up
Group									
Placebo	P	P	P	P	P	P	P	P	P
3 mg/kg q 8 wks	3	3	3	P	3	P	3	P	3
3mg/kg q 4 wks	3	3	3	3	3	3	3	3	3
10 mg/kg q 8 wks	10	10	10	P	10	P	10	P	10
10 mg/kg q 4 wks	10	10	10	10	10	10	10	10	10

3.2.3 Subjects

Major Eligibility Criteria. In addition to other eligibility criteria, patients considered eligible were to satisfy the following major entry criteria:

- Were diagnosed with rheumatoid arthritis at least 6 months prior to screening
- Had active disease as defined by:
  - ≥ 6 swollen joint
  - ≥ 6 tender joints
  - and at least 2 of the following: morning stiffness ≥ 45 mins, ESR ≥ 28 mm/h, CRP ≥ 20 mg/L
- The age limitations were ≥ 18 and ≤ 75 years
- Concurrent rheumatoid arthritis medications:
  - MTX - Were treated for at least 3 months with oral or parenteral MTX with no breaks in treatments of >2 weeks total during this period. Patients were to have been on a stable dose ≥ 12.5 mg/wk for at least 4 weeks prior to screening.
  - Folic acid – were treated with stable dose of folic acid prophylaxis for >4 weeks prior to screening
  - Oral corticosteroids – were receiving a stable dose ≤ 10 mg/day for at least 4 weeks prior to screening. Patients who were not using corticosteroids at the time of screening were not to have received them for at least 4 weeks prior to screening.
  - NSAIDs: Patients on NSAIDs (non-steroidal anti-inflammatory drugs) were to be on a stable dose for at least 4 weeks prior to screening. Patients who were not on NSAIDs were not to have received them for at least 4 weeks prior to screening.
- Laboratory results:
  - Hgb ≥ 5.3 mmol/L (≥ 8.5 g/dL), providing a low hemoglobin level was not due to nutritional deficiencies or due to diseases other than chronic rheumatoid arthritis,
  - WBC ≥ 3.5×10^9;
  - Neutrophils ≥ 1.5×10^9;
  - Platelets ≥ 100×10^9;
  - serum transaminase ≤ 2 times the upper limit of normal;
  - alkaline phosphatase levels ≤ 2 times the upper limit of normal;
  - serum creatinine ≤ 150 µmol/L (≤ 1.7 mg/dl).

Major exclusion criteria.

- Were incapacitated, largely or wholly bedridden or confined to a wheelchair, and had little or no ability for self-care.
- Used DMARDs, other than MTX within 4 weeks prior to screening
- Used intra-articular, intramuscular, or intravenous corticosteroids within 4 weeks prior to screening
- Previously received infliximab, cyclophosphamide, nitrogen mustard, chlorambucil, or other alkylating agent
- Had a history of the following infectious processes:
  - infected joint prosthesis within the previous 5 years
  - history of serious infections such as hepatitis, pneumonia, or pyelonephritis in the previous 3 months
  - chronic infectious disease such as chronic renal infection or chronic chest infection with bronchiectasis or sinusitis
  - had a history of active tuberculosis requiring treatment within the previous 3 years or history of opportunistic infections such as herpes zoster within the previous 2 months; had evidence of active cytomegalovirus, active pneumocystis carinii, or drug resistant atypical mycobacterium infections, etc.; or documented HIV/AIDS;
- Had a history of lymphoproliferative disease, including lymphoma and lymphadenopathy
- Had known malignancy or history of malignancy within the previous 5 years, except for squamous or basal cell carcinoma of the skin that were previously treated and had no evidence of recurrence.

3.2.4 Randomization and Maintenance of Blind

Patients were randomly assigned by the Randomization Center at [redacted] by using an adaptive stratified design with the investigational sites as the strata. The randomization center assigned each patient to a treatment group such that the number of patients in the 5 treatment groups was as balanced as possible within each investigational site, while maintaining a total of approximately 80 patients per treatment group.

Independent Joint Assessor. Each of the 68 joints included in the ACR joint set was to be evaluated for tenderness, and each of 66 joints was to be evaluated for swelling (hips were excluded for swelling). To maintain treatment blinding, an independent assessor was designated to perform all joint assessments at each study center. This individual was to have at least 2 years of experience in joint assessments and was required to have no other contact with the patient during the study, could not be the treating physician, could not discuss the patient's clinical status with the patient during the joint assessment or with other site personnel and was not permitted to review the patient's medical records, the CRF or any of the previous joint assessments.

Drug accountability. The pharmacist at the investigational site was unblinded to treatment assignment. Specially designated pharmacy monitoring consultants performed interim drug accountability and did the final drug reconciliation at all investigational sites. These individuals were unaffiliated with the sponsor, [redacted] or the study centers. They monitored the CRF pages provided to the pharmacist by [redacted] as part of the randomization procedure. These pages were collected and verified by [redacted] and were not sent to Centocor before any database lock.

Laboratory values. The post treatment CRP and RF results will not be released to the investigators by the central laboratories until the end of the study. The post treatment CRP and RF results were released to the sponsor after the week-30 database lock.

Results for antinuclear antibodies (ANAs) and anti-double-stranded DNA (dsDNA) antibodies will not be released to the investigators by the central laboratory until the end of the study. The results for ANA and anti-dsDNA antibodies were released to the sponsor after the week-30 database lock.

3.2.5 Concomitant Medications

Methotrexate. Patients were to be using oral or parenteral MTX for at least 3 months and on a stable dose of ≥ 12.5 mg/wk for 4 weeks prior to screening. The protocol allowed for decreases in MTX due to toxicity. If toxicity continued, MTX could be discontinued. If the toxicity resolved the MTX could be restarted at the investigator's discretion; if the toxicity continued with discontinuation of MTX, the study drug was discontinued.

Corticosteroids. Patients who were using oral corticosteroids were to receive a stable dose of ≤ 10 mg/day for at least 4 weeks prior to screening and were to continue this dose during the study. Intra-articular injections were allowed in a single joint; however, for the analyses of tender and swollen joints, this joint was to be considered as swollen and tender from the time of the first intra-articular injection onward.

NSAIDs. Patients who were using NSAIDs were required to be on a stable dose for at least 4 weeks before screening and to maintain the same dose throughout the study. The type or dose of NSAID was only to be changed in response to known side effects. For this trial, aspirin (except for low dose aspirin prescribed for cardiovascular disease) was considered an NSAID.

Change in medications defining loss of clinical response. The use of DMARDs other than MTX, or an increase in doses of MTX or corticosteroids above baseline levels, was considered a treatment failure.

However, patients who self-administered increased doses of oral steroids for a limited time, or who received increased doses of oral or parenteral steroids in error or for non-rheumatoid arthritis indications for a limited time, were not considered treatment failures for this medication change. Patients who received intra-articular injections of corticosteroids in more than one joint were considered nonresponders

as of the date that they received the injection into their second joint. Patients who received epidural injections of corticosteroids were also considered nonresponders thereafter.

3.2.6 Efficacy evaluations

The timepoints for the clinical assessments is shown in the study flowchart (Table 3.2).

Table 3.2 Study flowchart through week 54.

	Scr	Base line	wk 0	wk 2	wk 6	wk 10	wk 14	wk 18	wk 22	wk 26	wk 30	wk 34	wk 38	wk 42	wk 46	wk 50	wk 54
Randomization			X														
Chest X-ray	X																
Demographics/history	X																
EKG	X																
Physical exam	X										X						X
Weight			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Response[a]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of life		X				X					X			X			X
X-rays		X									X						X
C-reactive protein	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ESR	X										X						X
Rheumatoid factor			X			X					X						X
Routine laboratory	X			X	X		X		X		X		X		X		X
ANA			X	X	X	X		X		X		X		X		X	
Infliximab conc[b]			X	X	X		X		X		X		X		X		X
HACA			X														

[a] Clinical response at screening consisted of joint assessments and morning stiffness evaluations. Clinical response during the study periods were performed prior to the infusion of study drug.

[b] Blood for infliximab concentration was drawn prior to infusion and 1 hour after the end of the infusion.

The following clinical response assessments were performed:

- Joint assessment – each of 68 joints (ACR joint set) were evaluated for tenderness and 66 joints were evaluated for swelling, excluding hips. An independent assessor performed all joint assessments at each study site.

- Duration of morning stiffness – the average duration of morning stiffness during the previous week was assessed in minutes.

- VAS of pain – patients were asked to assess their average pain during the previous week on a VAS whose scale ranged from 0 to 10 cm.

- VAS of fatigue – same type of measurement as for pain.

- Patient and evaluator VAS of global disease assessment. The scale for the patient's assessment ranged from "very well" to "very poor". The scale for the evaluator's assessment ranged from "no arthritis activity" to "extremely active arthritis". The evaluator and patient were required to complete the global assessment independently from each other The results of the independent joint assessment were available to the evaluator assessing the patient's global disease.

- Disability index of the HAQ: the functional status of the patient was assessed by means of the disability index of the HAQ. The purpose of this 20-question instrument was to assess the degree of difficulty the patient had in accomplishing tasks in 8 functional areas (dressing, arising, eating,

walking, hygiene, reaching, gripping, and errands & chores). Responses in each area were scored from 0 (no difficulty) to 3 (inability to perform a task).

- Quality of life assessment: patients were assessed by using the SF-36 questionnaire. (The SF-36 is a health survey questionnaire consisting of 11 multi-item scales: limitations in physical functioning due to health problems, limitations in usual role activities due to physical health problems, bodily pain, general mental health (psychological distress and well being), limitations in usual role activities due to personal or emotional problems, limitations in social functioning due to physical or mental health problems, vitality (energy and fatigue) and general health perception. The concepts measured by the SF-36 are not specific to any age, disease, or treatment group).

- Hands and feet X-rays were obtained at week 30 but were not evaluated for this supplemental license application.

Follow-up evaluations. All patients were to return for efficacy and safety evaluations at weeks 30 and 54 regardless of whether they completed the entire treatment schedule or were continuing to respond to treatment. In addition, the investigator was to complete a questionnaire every 6 to 12 months for up to 3 years after the last infusion. For this long-term follow-up, patients will be asked to provide information regarding specific serious adverse events that occurred after the end of their participation in the clinical trial. Patients who discontinued study medication were strongly encouraged to return for week-30 and –54 evaluations.

3.2.7 Endpoint Definitions

Clinical Response. A clinical response was defined according to the ACR preliminary definition of improvement which required:

≥ 20% improvement in swollen joint count (66 joints) and tender joint count (68 joints)
and
≥ 20% improvement in 3 of the following 5 assessments:
- patient's assessment of pain (VAS)
- patient's global assessment of disease activity (VAS)
- evaluator's global assessment of disease activity (VAS)
- patient's assessment of physical function as measure by the HAQ
- CRP

Patients were considered to have achieved a clinical response if they satisfied the ACR preliminary definition of improvement without requiring initiation of or increases in medications for rheumatoid arthritis or a surgical joint procedure (i.e., arthrodesis and joint replacement).

Patients who were not required to continue scheduled efficacy evaluations for lack of efficacy because of the initiation of treatment with corticosteroids or a DMARD other than MTX, an increase in the dose of MTX or corticosteroids above baseline levels, or a surgical joint procedure that either involved any of the 68 joints in the ACR joint set or affected the assessment of one of those joints were considered nonresponders from the date of their withdrawal from the study (e.g., the date of the medication change or surgical procedure), regardless of their actual response data. In the primary analyses at week 30, patients who did not return for evaluation or who had insufficient data to assess their ACR status were considered nonresponders for clinical response. For all other patients, any data recorded were included in all data summaries and analyses.

If a patient had a surgical joint procedure in 1 of the joints included in the ACR joint set prior to his or her participation in the trial, those joints were not included in any of the joint assessments for this trial. Patients who had surgery, an intra-articular injection, or a needle aspiration on any of these joints during the study were included as responders if they satisfied the ACR criteria.

If a patients underwent intra-articular injections of corticosteroids or needle aspiration of fluid in a single joint included in the ACR joint set, that joint was considered tender and swollen thereafter. However, patients who received intra-articular injections of corticosteroids in more than 1 joint and/or needle aspiration of fluid from more than 1 joint were considered nonresponders as of the date that they received the injection or needle aspiration in their second joint. Patients who received epidural injections of corticosteroids were also considered nonresponders for the remainder of the trial.

For patients who had an incomplete joint set evaluated, the joint count was adjusted to a 68 joint count for pain/tenderness and a 66 joint count for swelling by dividing the number of affected joints by the number of joints evaluated and multiplying by 68 for pain/tenderness or 66 for swelling.

Patients who discontinued study treatment because of a safety reason (e.g., infusion reaction), but completed to 30-week follow-up evaluation and fulfilled all of the criteria for achieving a clinical response, were considered responders in the primary efficacy analysis.

Clinical remission. Patients were considered to have achieved a clinical remission if 5 of the following 6 requirements were fulfilled for at least 2 consecutive months (defined as 3 consecutive scheduled visits). This definition assumes that clinical remission occurred without an initiation of or increase in medications or an intervening (surgical) joint procedure as described for clinical response.

- Duration of morning stiffness did not exceed 15 minutes
- No fatigue (<0.5 cm on VAS)
- No joint pain (<0.5 cm on VAS)
- No joint tenderness or pain on motion
- No soft tissue swelling in joints or tendon sheaths
- CRP ≤ 10 mg/L

3.2.8 Primary Efficacy Analysis

The primary week-30 endpoint was the achievement of a clinical response at the week-30 follow-up visit. The primary analysis was performed on an intention-to-treat basis and compared the proportion of patients who achieved a clinical response in each of the infliximab treatment groups with that of the placebo group, i.e., MTX alone.

3.2.9 Secondary Efficacy Analyses

Secondary efficacy analyses were performed with patients included in the treatment groups to which they were randomly assigned.

Rapidity of response. The proportions of patients achieved a clinical response at the week-2 and evaluation were compared. Additionally, the proportion of patients who achieved a clinical response at the week 10 evaluation visit was compared among the groups.

Clinical response over time. The proportion of patients in each treatment group who achieved a clinical response at 5 or more of the maximum of 8 follow-up visits through week 30 were compared.

Differences in clinical benefit among the infliximab treatment groups. The weighted mean degree of clinical improvement for each of the individual ACR components were determined over the first 30 weeks of treatment. The weighted mean degree of clinical improvement was calculated for each patient on each of the individual components of the ACR criteria as the area under the clinical improvement versus time curve adjusted for the length of each follow-up visit and the value of the subsequent visit, divided by the total duration of observation. This procedure adjusts the area under the clinical improvement vs. time curve for the length of the patient's follow-up. Therefore, this type of analysis represent a per-patient average improvement of the 30-week follow-up period for each of the ACR criteria. These secondary endpoints will be referred to as an average degree of clinical improvement over time.

Comparison of the individual components of the ACR. The patients' assessments of morning stiffness and fatigue, and ESR values were summarized by treatment group at each visit, through week30. Summary statistics for percent change from baseline in rheumatoid factor (RF) was provided at each observation time by treatment group. Descriptive analysis of the differences among the treatment groups in percent change in RF from baseline to weeks 10 and 30 was also performed.

Improvements in ACR >20%. The proportion of patients who achieved improvements in the ACR criteria of <20%, 20% to <50%, 50% to <70%, 70% to <90%, or ≥ 90% were compared among the treatment groups at week 30. These also were compared among the treatment groups at week 2 and 10.

Consistency of treatment effect among patient groups. The plots of odds ratios with 95% confidence intervals were compared between all infliximab-treated patients combined with those of placebo for groups defined by demographic factors, baseline disease characteristics, and concomitant medications.

Quality of life. Summary statistics for SF-36 results were tabulated by treatment group over time.

3.3 Results

3.3.1 Patient Disposition

A total of 428 patients were enrolled at 34 study sites: 19 US, 3 Canadian and 12 European study sites. 12 of the 22 North American sites enrolled more than 10 patients (Table 3.3), 4 enrolled 10 patients and the remaining 6 sites enrolled >5 patients. Enrollment for the 30-week endpoint extended between March 31, 1997 and January 22, 1998 with the last 30-week evaluation occurring on August 31, 1998.

Table 3.3 North American sites that enrolled >10 patients

Site/Location	Number of Patients
Duke University Hospital Durham, NC	25
Virginia Mason Hospital Seattle, WA	22
Mt. Sinai Hospital Toronto, Ontario (Canada)	17
Hospital of the University of Pennsylvania Philadelphia, PA	16
Vanderbilt University Hospital and Clinic Nashville, TN	16
Clinical Research Center of Connecticut/NY Danbury, CT	15
University of Texas Southwestern Medical Center at Dallas, Dallas, TX	14
Charlton Medical Centre Hamilton, Ontario (Canada)	12
Rheumatology Associates of North Alabama Huntsville, AL	12
Arizona Rheumatology Center Phoenix, AZ	11
University of California San Diego Medical Center San Diego, CA	11
North Shore University Hospital Manhasset, NY	11

Distribution of Patients by Treatment Group. Of the 428 patients enrolled, 340 patients were randomly assigned to infliximab and 88 patients were assigned to receive treatment with placebo. The distribution of the patients are shown in Table 3.4.

Table 3.4 Distribution of patients to treatment group

	Placebo	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks	Total
Patients	88	86	86	87	81	428

Deviations in Treatment. There were 10 patients who received incorrect treatment for 1 or more infusions:

Placebo

23002 received 0.5 mg/kg infliximab at infusion 4 (week 10)
33009 received 0.5 mg/kg infliximab at infusion 3 (week 6)

3 mg/kg q 8 weeks

10005 received 0.5 mg/kg infliximab instead of placebo at the week-10 interim visit.
10007 received 0.5 mg/kg infliximab instead of placebo at the week-10 interim visit
22005 received 3 mg/kg infliximab instead of placebo at the week-18 interim visit
24002 received 3 mg/kg infliximab instead of placebo at the week-10 interim visit
26003 received placebo instead of 3 mg/kg at the week-22 visit. This patient also skipped the placebo infusion at the week-18 interim visit

10 mg/kg q 8 weeks

31005 received 0.5 mg/kg infliximab instead of placebo at the week-26 interim visit

10 mg/kg q 4 weeks

15010 received placebo instead of 10 mg/kg infliximab at the week-10 visit.
33015 received 6 incorrect treatments. The patient received 3 mg/kg of infliximab at the first 3 infusions and infusion 5, and placebo at infusions 4 and 6 because the randomization coordinator sent the incorrect treatment preparation forms to the pharmacist. This error was discovered after the week-18 infusion and was corrected for infusions 7 and 8.

For the efficacy and study populations analyses, the sponsor included all patients in the treatment group to which they were randomly assigned. Because of the substantial deviations for patients 23002, 33009 (both placebo), and 33015, the sponsor placed these patients into the 3 mg/kg q 8 weeks treatment group for the safety analysis.

Study entry criteria violations. There were 49 patients enrolled who did not meet the entry criteria:

- 11 patients were not on stable doses of folic acid prophylaxis for at least 4 weeks prior to screening.
- 1 patients who was not a stable dose of steroids
- 1 patient who was not on a stable dose of NSAIDs
- 2 patients who received an alkylating agent (cyclophosphamide) prior to study entry
- 2 patients who had received another investigational drug within the 2 months prior to enrollment
- 3 patients who were more than 75 years of ages
- 2 patients who were enrolled with abnormal liver enzymes laboratory values
- 1 patients did not sign the informed consent until after screening but did prior to receipt of study drug
- 7 patients did not meet the entry criteria regarding MTX: one patient enrolled at a dose of 10 mg/kg, 3 patients were not on a stable dose, 1 patient had an interruption in therapy for more than 2 weeks, and 2 patients were on MTX therapy for less than 3 months prior to enrollment
- 22 patients who did not meet the active disease entry criteria: 4 did not meet the criteria for ≥ 6 swollen and tender joints, 17 did not qualify for 2 of the CRP, ESR, and morning stiffness criteria and 1 patient did not meet the criteria for both the ≥ 6 swollen and tender joints and 2 of three ACR criteria. The distribution among the treatment groups for this violation was 1 patient in placebo, 4 in the 3 mg/kg q 8 week group, 8 patients in the 3 mg/kg q 4 weeks, 3 patients in the 10 mg/kg q 8 weeks group, and 6 patients in the 10 mg/kg q 4 weeks group.

Patients lost to follow-up. There were two patients (02009 and 20011) who were lost to follow-up through week 30 because of the patients' distance from the study site.

3.3.1.1 Patient Demographics

The majority of the patients enrolled into T22 were women (77.6%). Of the 428 patients, 389 (90.9%) were white and the remaining patients were black (5.1%), Asian (0.7%), or "other" (3.3%). The median age of the patients was 53.5 (range: 19 to 80 years).

Baseline Patient Characteristics. The baseline disease characteristics for the efficacy variables were balanced across all treatment groups (Table 3.5). For all patients enrolled, the median duration of

rheumatoid arthritis was 8.4 years (range: 0.5 to 49.9 years), which was relatively short considering the advanced stages of rheumatoid arthritis in these patients.

Table 3.5 Baseline Disease Characteristics

	Placebo	3 mg/kg q 8	3 mg/kg q 4	10 mg/kg q 8	10 mg/kg q 4
Number of swollen joints (0-66)					
mean ± SD	22 ± 12	22 ± 12	21 ± 11	23 ± 13	24 ± 12
median	19	19	20	20	23
Number of Tender joints (0-68)					
mean ± SD	31 ± 18	32 ± 18	31 ± 15	32 ± 16	34 ± 16
median	24	32	31	30	35
Pain (VAS, 0-10 cm)					
mean ± SD	6.3 ± 2.2	6.8 ± 19.9	6.2 ± 2.3	6.6 ± 1.7	6.2 ± 2.1
median	6.7	7.0	6.9	6.7	6.6
Evaluator's global (VAS)					
mean ± SD	6.2 ± 1.7	6.0 ± 1.8	6.0 ± 1.9	6.1 ± 1.8	5.9 ± 1.7
median 6.5	6.5	6.1	6.2	6.4	6.0
Patient's global (VAS)					
mean ± SD	6.0 ± 2.5	6.4 ± 2.2	5.9 ± 2.4	6.3 ± 1.9	5.9 ± 2.4
median	6.2	6.6	5.7	6.4	6.0
HAQ disability index (0-3)					
mean ± SD	1.7 ± 0.6	1.8 ± 0.6	1.7 ± 0.6	1.7 ± 0.6	1.7 ± 0.6
median	1.8	1.8	1.8	1.8	1.6
CRP (mg/dL)					
mean ± SD	4.0 ± 4.2	3.9 ± 3.4	3.5 ± 4.2	3.3 ± 3.4	4.2 ± 4.3
median	3.0	3.1	2.0	2.5	2.4
Duration of morning stiffness (min)					
mean ± SD	199 ± 279	164 ± 248	186 ± 263	226 ± 317	181 ± 281
median	120	90	120	120	120
Fatigue (VAS)					
mean ± SD	6.1 ± 2.3	6.2 ± 2.2	6.5 ± 2.2	6.4 ± 1.9	6.6 ± 2.2
median	6.7	6.5	7.1	6.7	6.8

A total of 37.4% of patients had had prior joint surgery (14.7% had synovectomy, 13.3% had arthrodesis, and 23.1% had joint replacement). 80.8% of the patients were positive for rheumatoid factor. 43.0% had extra-articular manifestations of rheumatoid arthritis at baseline. The majority (35.3%) had rheumatoid nodules as the extra-articular manifestation of rheumatoid arthritis. Approximately 6% of patients had Sjogren's syndrome at baseline, which is lower than the 10-20% incidence generally observed in rheumatoid arthritis patients. The incidence of vasculitis and interstitial lung fibrosis was relatively low (0.2% and 1.9%, respectively).

Prior and concomitant medications. Table 3.6 shows the history of DMARDs including MTX prior to enrollment. There were no significant differences among the treatment groups in the prior use of DMARDs. 374 (87.4%) patients had been treated with 1 or more DMARD besides MTX prior to enrollment. The most common DMARDs received were gold preparations (63.4%), sulfasalazine (58%), and hydroxychloroquine (54%). The majority of patients (50.9%) had received MTX therapy for a duration of ≥ 3 years; 34.6% of patients had received MTX therapy for ≥ 1 to <3 years and 14.5% of patients had received therapy for <1 year. Information on the cumulative MTX dose was obtained by the investigator as an estimate of the sum of all MTX received by a patient since that patient began MTX therapy.

Table 3.6 History of Disease Modifying Antirheumatic Drugs (DMARDS)

	Placebo	3 mg/kg q 8	3 mg/kg q 4	10 mg/kg q 8	10 mg/kg q 4
Pts randomized	88	86	86	87	81
Patients w/hx DMARDs other than MTX					
	79 (89.8%)	75 (87.2%)	76 (88.4%)	70 (80.5%)	74 (91.4%)
Total number of prior DMARDs other than MTX					
mean ± SD	2.5 ± 1.4	2.8 ± 1.5	2.6 ± 1.5	2.5 ± 1.4	2.5 ± 1.3
median	2	3	2	2	2
Patients who used ≥ 1 DMARD					
Gold	47 (59.5%)	47 (62.7%)	48 (63.2%)	43 (61.4%)	52 (70.3%)
Hydroxychloroquine	40 (50.6%)	42 (56%)	46 (60.5%)	36 (51.4%)	38 (51.4%)
Chloroquine	14 (17.7%)	9 (12%)	12 (15.8%)	10 (14.3%)	8 (10.8%)
Sulfasalazine	47 (59.5%)	51 (68%)	42 (55.3%)	41 (58.6%)	36 (48.6%)
Penicillamine	23 (29.1%)	20 (26.7%)	14 (18.4%)	22.916	16 (21.6%)
Azathioprine	11 (13.9%)	18 (24%)	19 (25%)	13 (18.6%)	15 (20.3%)
Cyclosporine	12 (15.2%)	17 (22.7%)	12 (15.8%)	14 (20%)	15 (20.3%)
Other	2 (2.5%)	8 (10.7%)	4 (5.3%)	3 (4.3%)	5 (6.8%)
Note: denominator is number of patients w/hx DMARD other than MTX					
Duration of MTX therapy					
<1 year	12 (13.6%)	15 (17.4%)	15 (17.4%)	10 (11.5%)	10 (12.3%)
≥ 1 year to <3 years	32 (36.4%)	29 (33.7%)	31 (36%)	30 (34.5%)	26 (32.1%)
≥ 3 years	44 (50%)	42 (48.8%)	40 (46.5%)	47 (54%)	45 (55.6%)
Cumulative MTX dose (mg)					
<1000	34 (38.6%)	30 (34.9%)	34 (39.5%)	25 (28.7%)	27 (33.3%)
≥ 1000 to <2000	14 (15.9%)	19 (22.%)	22 (25.6%)	25 (28.7%)	13 (16%)
≥ 2000 to <3000	14 (15.9%)	10 (11.6%)	7 (8.1%)	12 (13.8%)	13 (16%)
≥ 3000	26 (29.5%)	27 (31.4%)	23 (26.7%)	25 (28.7%)	28 (34.6%)

Note: The maximum dose of MTX within the 3 and 6 months prior to enrollment was 15 mg for all dose groups. The median dose of MTX at baseline was 15 mg for all dose groups.

Discontinuations. Appendix 3.A lists the patients by their identification number and the reasons for their discontinuations. Table 3.7 summarizes the number of patients who received each infusion to week 30, the number of patients who discontinued treatment, i.e., did not receive subsequent infusions, and the reasons for their discontinuations. This table includes patients who discontinued study treatment after infusion 8 (week 26) but before or at week 30. The number of patients who discontinued treatment was highest among patients who received placebo (36.4%) and was primarily due to lack of efficacy. For all of the infliximab treated patients, 45 (13.3%) discontinued therapy: 16 (5.7%) due to adverse events and 27 (7.9%) due to lack of efficacy. Although there was no statistical difference in the reasons for discontinuations in the infliximab treated patients, slightly more discontinued due to adverse events at the 10 mg/kg q 4 week group and more patients discontinued due to lack of efficacy in the 3 mg/kg q 8 week group resulting in more patients completing the 30 week course in the 3 mg/kg q 4 week and 10 mg/kg q 8 week groups.

Table 3.7 Patients who received and discontinued study treatment through week 30.

	Placebo	3 mg/kg q 8 weeks	3 mg/kg q 4 weeks	10 mg/kg q 8 weeks	10 mg/kg q 4 weeks
Patients randomized	88	86	86	87	81
Number of patients infused					
#1 (wk 0)	88 (100%)	86 (100%)	86 (100%)	87 (100%)	81 (100%)
#2 (wk 2)	88 (100%)	86 (100%)	86 (100%)	87 (100%)	81 (100%)
#3 (wk 6)	82 (93.2%)	84 (97.7%)	84 (97.7%)	86 (98.9%)	80 (98.8%)
#4 (wk 10)	71 (80.7%)	82 (95.3%)	81 (94.2%)	85 (97.7%)	78 (96.3%)
#5 (wk 14)	66 (75%)	81 (94.2%)	81 (94.2%)	83 (95.4%)	78 (96.3%)
#6 (wk 18)	62 (70.5%)	77 (89.5%)	79 (91.9%)	82 (94.3%)	73 (90.1%)
#7 (wk 22)	58 (65.9%)	75 (87.2%)	77 (89.5%)	81 (93.1%)	71 (87.7%)
#8 (wk 26)	58 (65.9%)	72 (83.7%)	77 (89.5%)	80 (92%)	69 (85.2%)
Number of pts who discontinued	32 (36.4%)	15 (17.4%)	10 (11.6%)	8 (9.2%)	12 (14.8%)
Reasons for discontinuation					
Adverse Event	7	3	4	3	6
Lack of Efficacy					
no Δ med	7	7	4	3	2
Δ med/surgery	15	4	2	2	3
Other	3	1	0	0	1

3.3.2 Efficacy Results

3.3.2.1 Primary endpoint

The primary clinical endpoint was a clinical response defined by an ACR 20% response without a protocol-prohibited change in medication and/or surgical joint procedure at 30 weeks. The primary analysis was conducted on patients randomized to their treatment group even though they may have had discrepancies to that dosing regimen. Analysis of the overall treatment effect showed statistically significant differences among treatment groups and pairwise comparisons showed that the response rate for each infliximab treatment group was statistically significant compared to placebo (Table 3.8).

Table 3.8 Number of patients who achieved a clinical response at 30 weeks

	Placebo	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks	Treatment effect p-value
Pts randomized	88	86	86	87	81	
Responders	18 (20.5%)	43 (50.0%)	43 (50.0%)	45 (51.7%)	47 (58.0%)	<0.0001
p-value vs. placebo		<0.001	<0.001	<0.001	<0.001	

The sponsor conducted 5 analyses of the clinical response to examine the robustness of the primary analysis at 30 weeks. None of these analyses changed any of the conclusions based upon the primary analysis, i.e., both the overall treatment effect and pairwise comparisons for each treatment group with placebo were statistically significant.

- Number of patients who achieved a clinical response at week 30 visit, with patients considered non-responders who discontinued study treatment because of adverse event

- Number of patients who achieved a clinical response at week 30 visit, with patients considered non-responders who discontinued because of lack of efficacy (but did not have a protocol prohibited change in medication or a surgical joint procedure).

- Number of patients who achieved a clinical response at week 30 visit but were considered non-responders because of lack of efficacy or discontinuation because of adverse event (but did not have a protocol prohibited change in medication or surgical joint procedure).

- Number of patients who achieved clinical response at week 30 visit with no adjustment for protocol-prohibited changed in medication and/or surgical joint procedures.

- Number of patients who achieved a clinical response at week 30 visit with patients in q 8 week dosing groups who received infliximab on a visit when scheduled to receive placebo considered as non-responders.

3.3.2.2 Secondary Efficacy Analyses

Secondary efficacy analyses were performed with patients included in the treatment groups to which they were randomly assigned using the actual data collected. Patients with insufficient data to make an assessment were not included in patients evaluated, except for patients who had previously discontinued because of lack of efficacy who were classified as nonresponders.

Rapidity of response. The proportions of patients who achieved a clinical response at the week-2 and evaluation were compared. Additionally, the proportion of patients who achieved a clinical response at the week 10 evaluation visit was compared among the groups.

The number of patients who achieved a clinical response at a given visit through week 30 is shown in Table 3.9. Since the dosing schedule for all infliximab regimens were identical through week 10, the two 3 mg/kg and two 10 mg/kg dosing groups can be combined. Comparison of their response for each of these doses compare to placebo at both week 2 and week 10 were statistically significant both on the treatment effect and for the individual group comparisons. Patients in all of the treatment groups showed a rapid clinical response by week 2 which gradually increased through week 14 after which the proportion of patients who experienced a clinical response at subsequent visits was fairly constant except for the 3 mg/kg q 8 week dosing group where the number of responders appeared to increase through week 22 before remaining fairly constant.

Table 3.9 Number of patients who achieved a clinical response at specified visits through week 30[a]

	Placebo	3 mg/kg q 8	3 mg/kg q 4	10 mg/kg q 8	10 mg/kg q 4
Pts randomized	88	86	86	87	81
Time after initial infusion					
Week 2					
Pts evaluated	88	86	85	87	81
Pts responded	5 (5.7%)	25 (29.1%)	22 (25.9%)	28 (32.2%)	23 (28.4%)
Week 6					
Pts evaluated	88	84	84	85	80
Pts responded	16 (18.2%)	36 (42.9%)	41 (48.8%)	40 (47.1%)	36 (45%)
Week 10					
Pts evaluated	82	81	84	85	80
Pts responded	15 (18.3%)	35 (43.2%)	34 (40.5%)	44 (51.8%)	33 (41.3%)
Week 14					
Pts evaluated	81	83	86	85	78
Pts responded	16 (19.8%)	35 (42.2%)	38 (44.2%)	42 (49.4%)	45 (57.7%)
Week 18					
Pts evaluated	82	80	85	82	76
Pts responded	17 (20.7%)	38 (47.5%)	40 (47.1%)	47 (57.3%)	43 (56.6%)
Week 22					
Pts evaluated	80	83	84	86	73
Pts responded	18 (22.5%)	45 (54.2%)	43 (51.2%)	47 (54.7%)	42 (57.5%)
Week 26					
Pts evaluated	81	83	83	85	77
Pts responded	17 (21%)	40 (48.2%)	48 (57.8%)	53 (62.4%)	48 (62.3%)
Week 30					
Pts evaluated	84	83	85	85	80
Pts responded	18 (21.4%)	43 (51.8%)	43 (50.6%)	45 (52.9%)	47 (58.8%)

[a] Patients who discontinued regularly scheduled efficacy evaluations because of lack of efficacy were considered non-responders. However, if discontinuation was because of an adverse event of "other" reason (e.g., consent withdrawn), then the patient was excluded from "Pts evaluated". If data were available (including the week 30 visit), the assessment was based upon the data available.

Clinical response over time. The proportion of patients in each treatment group who achieved a clinical response at 5 or more of the maximum of 8 follow-up visits through week 30 were compared. These 5 visits need not have been consecutive. A total of 141 (41.5%) of the 340 patients treated with infliximab achieved a clinical response at ≥ 5 visits compared with only 11 (12.5%) of the 88 patients in the placebo group (overall treatment effect p-value <0.001). (Table 3.10). These results were similar to those results from an analysis where patients who discontinued study treatment because of an adverse event were classified as non-responders for all visits, i.e., achieved a clinical response at 0 visits.

Table 3.10 Number of patients who achieved a clinical response over time by the total number of visits through week 30.

	Placebo	3 mg/kg q 8	3 mg/kg q 4	10 mg/kg q 8	10 mg/kg q 4
Pts randomized	88	86	86	87	81
Pts w/response ≥ 5 visits					
	11 (12.5%)	28 (32.6%)	35 (40.7%)	42 (48.3%)	36 (44.4%)
p vs. placebo		0.002	<0.001	<0.001	<0.001
Patients w/response at each visit by total visits					
8 visits	0	7 (8.1%)	11 (12.8%)	9 (10.3%)	10 (12.3%)
7 visits	1 (1.1%)	10 (11.6%)	6 (7%)	14 (16.1%)	9 (11.1%)
6 visits	2 (2.3%)	6 (7%)	10 (11.6%)	10 (11.5%)	10 (12.3%)
5 visits	8 (9.1%)	5 (5.8%)	8 (9.3%)	9 (10.3%)	7 (8.6%)
4 visits	4 (4.5%)	15 (17.4%)	8 (9.3%)	8 (9.2%)	7 (8.6%)
3 visits	7 (8%)	9 (10.5%)	6 (7%)	6 (6.9%)	12 (14.8%)
2 visits	6 (6.8%)	9 (10.5%)	9 (10.5%)	7 (8%)	4 (4.9%)
1 visit	14 (15.9%)	5 (5.8%)	11 (12.8%)	7 (8%)	7 (8.6%)
0 visits	46 (52.3%)	20 (23.3%)	17 (19.8%)	17 (19.5%)	15 (18.5%)

Differences in clinical benefit among the infliximab treatment groups. The analyses of the average degree of improvement over time in the ACR components were performed to evaluate whether or not any differences occurred between doses or between dosing intervals, and whether or not there was an interaction between these two factors. These AUC-type analyses were performed as average degree of clinical improvement over time. These endpoints represent a per patient average improvement over the 30-week follow-up period for each of the ACR criteria. These analyses were performed only on the infliximab treated patient groups.

Table 3.11 shows the average degree of clinical improvement from baseline through week 30 in the individual ACR components. There was an improvement in all of the ACR components with medians ranging between 35 and 49, except for HAQ with a lower median range of 14 to 20 and CRP with a higher median range of 50-59.

Although both the dose and dosing schedules were similarly efficacious in reducing the signs and symptoms of rheumatoid arthritis, there is a mild indication of dose response as the doses and frequency of treatment increases, except for the patient's assessment of pain and disease activity. Interestingly, the median change in the more objective assessment of disease activity, i.e., swollen and tender joints and CRP, is slightly higher than the more subjective assessments by the patients including the HAQ. The evaluator's assessment of disease activity corresponds more with the objective assessments, perhaps because their assessment is based upon more objective findings. A similar analysis on the 54 week data will be useful in order to determine whether or not the patient's subjective assessments will increase with time in conjunction with continued improvement of their swollen and tender joints.

Table 3.11 Average degree of clinical improvement from baseline in the ACR components through week 30[a].

	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks
Pts randomized	86	86	87	81
Swollen joints				
Mean ± SD	37 ± 24	40 ± 23	42 ± 23	44 ± 23
Median	35%	41%	43%	49%
Tender joints				
Mean ± SD	41 ± 25	42 ± 28	46 ± 26	47 ± 26
Median	38%	47%	46%	46%
Pts assessment of pain				
Mean ± SD	36 ± 25	38 ± 26	43 ± 27	38 ± 27
Median	36%	36%	40%	35%
Pts assessment of disease activity				
Mean ± SD	36 ± 25	36 ± 25	41 ± 26	38 ± 26
Median	36%	35%	39%	36%
Evaluator's assessment of disease activity				
Mean ± SD	40 ± 24	44 ± 26	42 ± 26	44 ± 23
Median	42%	45%	45%	46%
HAQ				
Mean ± SD	21 ± 21	26 ± 25	31 ± 29	24 ± 25
Median	14%	20%	19%	16%
CRP				
Mean ± SD	50 ± 29	52 ± 29	52 ± 26	54 ± 28
Median	50%	58%	54%	59%

[a] Patients who discontinued regularly scheduled efficacy evaluations or who were non-responders because of a protocol-prohibited change in medication and/or a surgical joint procedure had their area under the curve measurement truncated (set to 0% improvement) at the time they discontinued efficacy evaluations or had the medication change or surgical procedure.

Comparison of the individual components of the ACR. Appendix 3.B contains tables that summarize the median and median percent change from baseline for each of the individual clinical and laboratory variables (including rheumatoid factor) measured as well as fatigue and duration of morning stiffness. For each of the individual variables patients treated with any dose or dosing regimen of infliximab had a greater percent improvement of their symptoms or laboratory values compared to placebo. The improvement was seen in both the objective and more subjective clinical variables. Although patients treated with 3 mg/kg q 8 weeks of infliximab had a better response compared to placebo, review of these tables suggest that there is a dose response with patients receiving higher doses experiencing a greater median percentage improvement. It is also interesting to note, that the percentage change tended to be overall higher in the more objective clinical and laboratory variables than in the subjective variables. Similar to the analyses of the average degree of improvement over time in the ACR components described previously, the least response was seen with improvement of HAQ while the greatest degree of improvement was shown in CRP measurement.

The time to improvement was similar to the previous evaluations of the primary and other secondary endpoints. Improvement was seen in all infliximab dosing groups by week 2 and begin to level off by week 14 except for the 3 mg/kg q 8 week dosing group where the leveling off tended to occur by the fourth infusion at week 18.

Improvements in ACR >20%. Table 3.12 compares the proportion of patients who achieved improvements in the ACR criteria of <20%, 20% to <50%, 50% to <70%, 70% to <90%, or ≥ 90% among the treatment groups at week 30. Comparison of the treatment groups at week 2 and 10 shows that more patients treated with infliximab achieved ACR >20% at the earlier timepoints. Table 3.12 also shows the number of

patients who achieved a clinical remission through week 30 as defined by fulfilling Pinals criteria for at least 2 consecutive months.

Table 3.12 Number of patients who achieved various degrees of ACR response at the week 30 visit

	Placebo	3 mg/kg q 8 weeks	3 mg/kg q 4 weeks	10 mg/kg q 8 weeks	10 mg/kg q 4 weeks
Pts randomized	88	86	86	87	81
Pts evaluated	84	83	85	85	80
ACR <20%	66 (78.6%)	40 (48.2%)	42 (49.4%)	40 (47.1%)	33 (41.3%)
ACR 20% to <50%	14 (16.7%)	21 (25.3%)	18 (21.2%)	19 (22.4%)	26 (32.5%)
ACR 50% to <70%	4 (4.8%)	15 (18.1%)	16 (18.8%)	11 (12.9%)	12 (15%)
ACR 70% to <90%	0	5 (6%)	8 (9.4%)	9 (10.6%)	7 (8.8%)
ACR 90% to 100%	0	2 (2.4%)	1 (1.2%)	6 (7.1%)	2 (2.5%)
Remission[a]	0	1 (1.2%)	1 (1.2%)	1 (1.1%)	0

[a] Patients were considered to have achieved a clinical remission if they fulfilled the Pinals criteria for at least 2 consecutive months (defined as 3 consecutive visits).

Consistency of treatment effect among patient groups. The plots of odds ratios with 95% confidence intervals were compared between all infliximab-treated patients combined with those of placebo for groups defined by demographic factors, baseline disease characteristics, and concomitant medications. Overall, for all of the various analyses, the odds that patients treated with infliximab would respond were greater than for patients treated with placebo. The odds that patients with anatomical stage I disease and functional class I disease treated with infliximab would respond were not significantly greater than the odds for response in patients treated with placebo. However, the number of patients in each subgroup were small with wide 95% confidence intervals and it should be noted that the odds of a response was greater in patients treated with infliximab for the other baseline characteristics, e.g., the number of swollen and tender joints. Regarding gender, the odds that males responded to treatment with infliximab was not significantly greater than response when treated with placebo. Again, this lack of greater effect may be due to the lower number of males in the treatment groups rather than a true gender difference

Quality of life. Summary statistics for SF-36 results were tabulated by treatment group over time. The SF-36 questionnaire has an 8-scale scores for Physical Function, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional and Mental Health scales, and 2 summary scales (Physical Component summary and Mental Component summary).

Comparison between patients treated with placebo and infliximab of the physical component summary showed greater improvement in patients treated with infliximab. At baseline, the median value at baseline was approximately 25; the median value for the general US population (healthy without a chronic medical condition) is 55.8. At week 30, patients treated with infliximab had a median score of 33.0 while patients treated with placebo had a median score of 28.3. These 30-week median scores are not statistically significant (p=0.063). The treatment effect was driven primarily by improved physical functioning and bodily pain scales of the SF-36.

Comparison between the two treatments for the SF-36 mental component summary showed no difference in improvement. At baseline, the study patient median score was approximately 48; the median for the healthy US population is 54.7. At week 30, the median value for patients treated with infliximab was approximately 53 whereas patients treated with placebo had a median value of 55.4. The improvement seen in the study population was driven primarily by the social functioning scale and somewhat by the vitality scale of the SF-36.

3.3.2.3 Conclusions regarding the Efficacy Data of T22

- All of the dosing regimens evaluated in the pivotal trial, T22, showed benefit as adjunctive therapy to MTX in the treatment of patients with rheumatoid arthritis. There was no apparent dose response effect among the four dose regimens of infliximab evaluated but a slightly greater proportion of patients responded by the ACR 20 criteria to the higher dose, 10 mg/kg q 4 weeks.

- The benefit shown using the primary endpoint of ACR 20 is supported by analyses of the secondary endpoints.

3.3.3. Review of Safety Data in T22 (ATTRACT)

This section summarizes the available safety data regarding patients enrolled into T22. Patients continued to be treated in T22 after the 30 week endpoint for signs and symptoms and the clinical data were analyzed again at 54 week for effect of infliximab upon structural damage. During the review of the 30-week data, the sponsor submitted a summary analysis of the blinded safety data through the week 52 timepoint. Most of the additional safety data submitted had gone through an initial cleaning process so it should be kept in mind that some of the data may not be completely accurate. A complete review of the unblinded 52 week safety data will be done when the data are submitted. The sponsor also submitted a more complete review of the serious infections that occurred through 54 weeks during the review process. All of these available safety data will be summarized in this review and I will note where only 30 week data is available for review.

In the 54-week database, 304 of 428 patients had received study drug through week 54, i.e., received the week 54 infusion. Of these, 264 patients received infliximab through week 54. Safety data for all patients originally enrolled are included since all patients were followed through week 54, even if they had discontinued treatment with study agent. In the 30 week database, 351 of 428 patients received study drug through week 30, i.e., received week 30 infusion. Of these, 295 patients received infliximab through week 30.

Three patients were analyzed for safety in a treatment group that more closely resembled the actual treatment that they received rather than the treatment group to which they were randomly assigned. Patients 23002 and 33009 were randomized to placebo but received 0.5 mg/kg infliximab for one infusion each and are included in the 3 mg/kg q 8 weeks treatment group. Patient 33015 was randomized to 10 mg/kg q 4 weeks but received 6 treatments in accordance more with the 3 mg/kg q 8 week cohort. Consequently, the numbers of patients in each treatment group cited for the efficacy analysis differ from those in the safety analysis for these cohorts.

3.3.3.1 Adverse events

All Adverse Events

Table 3.13 summarizes the numbers of patients with ≥ 1 adverse event by WHOART system-organ class and preferred term. The table reports events for each system and only those adverse events by organ that occurred in ≥ 5% patients receiving any dose regimen of infliximab in order to detect any dose response. An event related to a major safety concern may be reported even if the event occurred in <5% patients.

Table 3.13 Number of patients with any adverse event through week 54 by WHOART and preferred term

	Placebo	3 mg/kg q 8 weeks	3 mg/kg q 4 weeks	10 mg/kg q 8 weeks	10 mg/kg q 4 weeks	All Infliximab
Pts randomized	86	89	86	87	80	342
Avg. weeks follow-up	49.1	51.0	53.8	53.5	53.6	53.0
Pts with ≥ 1 event	81 (94.2%)	82 (92.1%)	79 (91.9%)	85 (97.7%)	78 (97.5%)	324 (94.7%)
Respiratory Disorders	**41 (47.7%)**	**57 (64.0%)**	**49 (57.0%)**	**57 (65.5%)**	**49 (61.3%)**	**212 (62.0%)**
Upper infection	19 (22.1%)	35 (39.3%)	23 (26.7%)	33 (37.9%)	24 (30.0%)	115 (33.6%)
Sinusitus	5 (5.8%)	17 (19.1%)	10 (11.6%)	17 (19.5%)	14 (17.5%)	58 (17.0%)
Coughing	6 (7.0%)	10 (11.2%)	9 (10.5%)	17 (19.5%)	14 (17.5%)	50 (14.6%)
Pharyngitis	5 (5.8%)	7 (7.9%)	7 (8.1%)	11 (12.6%)	12 (15.0%)	37 (10.8%)
Rhinitis	9 (10.5%)	9 (10.1%)	5 (5.8%)	12 (13.8%)	9 (11.3%)	35 (10.2%)
Bronchitis	7 (8.1%)	6 (6.7%)	8 (9.3%)	3 (3.4%)	7 (8.8%)	24 (7.0%)
Dyspnea	2 (2.3%)	3 (3.4%)	3 (3.5%)	7 (8.0%)	5 (6.3%)	18 (5.3%)
Pneumonia	2 (2.3%)	0	4 (4.7%)	3 (3.4%)	2 (2.5%)	9 (2.6%)

Table 3.13 (cont'd) Number of patients with any adverse event through week 54 by WHOART and preferred term

	Placebo	3 mg/kg q 8 weeks	3 mg/kg q 4 weeks	10 mg/kg q 8 weeks	10 mg/kg q 4 weeks	All Infliximab
Gastrointestinal Disorders	**40 (46.5%)**	**38 (42.7%)**	**45 (52.3%)**	**46 (52.9%)**	**48 (60.0%)**	**177 (51.8%)**
Nausea	18 (20.9%)	17 (19.1%)	16 (18.6%)	17 (19.5%)	15 (18.8%)	65 (19.0%)
Diarrhea	14 (16.3%)	11 (12.4%)	13 (15.1%)	12 (13.8%)	14 (17.5%)	50 (14.6%)
Abdominal pain	8 (9.3%)	7 (7.9%)	12 (14.0%)	10(11.5%)	8 (10.0%)	37 (10.8%)
Stomatitis ulcerative	3 (3.5%)	7 (7.9%)	6 (7.0%)	5 (5.7%)	11 (13.8%)	29 (8.5%)
Dyspepsia	6 (7.0%)	6 (6.7%)	6 (7.0%)	4 (4.6%)	10 (12.5%)	26 (7.6%)
Vomiting	10 (11.6%)	4 (4.5%)	6 (7.0%)	7 (8.0%)	8 (10.0%)	25 (7.3%)
Gastroenteritis	3 (3.5%)	4 (4.5%)	5 (5.8%)	4 (4.6%)	2 (2.5%)	15 (4.4%)
Constipation	5 (5.8%)	4 (4.5%)	2 (2.3%)	4 (4.6%)	3 (3.8%)	13 (3.8%)
GE reflux	1 (1.2%)	3 (3.4%)	1 (1.2%)	2 (2.3%)	4 (5.0%)	10 (2.9%)
Skin Disorders	**30 (34.9%)**	**33 (37.1%)**	**40 (46.5%)**	**37 (42.5%)**	**40 (50.0%)**	**150 (43.9%)**
Rash	5 (5.8%)	7 (7.9%)	11(12.8%)	18 (20.7%)	12 (15.0%)	48 (14.0%)
Pruritus	0	5 (5.6%)	8 (9.3%)	4 (4.6%)	5 (6.3%)	22 (6.4%)
Urticaria	0	4 (4.5%)	2 (2.3%)	4 (4.6%)	5 (6.3%)	15 (4.4%)
Sweating increased	0	2 (2.2%)	5 (5.8%)	4 (4.6%)	3 (3.8%)	14 (4.1%)
Erythema	1 (1.2%)	1 (1.1%)	3 (3.5%)	5 (5.7%)	2 (2.5%)	11 (3.2%)
Skin wound	2 (2.3%)	1 (1.1%)	3 (3.5%)	2 (2.3%)	4 (5.0%)	10 (2.9%)
Dermatitis	0	2 (2.2%)	3 (3.5%)	0	4 (5.0%)	9 (2.6%)
Dermatitis fungal	3 (3.5%)	2 (2.2%)	0	5 (5.7%)	1 (1.3%)	8 (2.3%)
Central & peripheral nervous system disorders	**30 (34.9%)**	**32 (36.0%)**	**35 (40.7%)**	**39 (44.8%)**	**37 (46.3%)**	**143 (41.8%)**
Headache	14 (16.3%)	24 (27.0%)	22 (25.6%)	22 (25.3%)	22 (27.5%)	90 (26.3%)
Dizziness	10 (11.6%)	8 (9.0%)	8 (9.3%)	14 (16.1%)	7 (8.8%)	37 (10.8%)
Paresthesia	4 (4.7%)	1 (1.1%)	5 (5.8%)	4 (4.6%)	4 (5.0%)	14 (4.1%)
Muscle contractions involuntary	0	3 (3.4%)	2 (2.3%)	5 (5.7%)	4 (5.0%)	14 (4.1%)
Hypesthesia	0	2 (2.2%)	1 (1.2%)	3 (3.4%)	4 (5.0%)	10 (2.9%)
Body as a whole Disorders	**28 (32.6%)**	**33 (37.1%)**	**32 (37.2%)**	**30 (34.5%)**	**36 (45.0%)**	**131 (38.3%)**
Fatigue	6 (7.0%)	16 (18.0%)	8 (9.3%)	5 (5.7%)	12 (15.0%)	41 (12.0%)
Pain	9 (10.5%)	8 (9.0%)	8 (9.3%)	11 (12.6%)	9 (11.3%)	36 (10.5%)
Chest Pain	6 (7.0%)	5 (5.6%)	5 (5.8%)	7 (8.0%)	6 (7.5%)	23 (6.7%)
Edema peripheral	7 (8.1%)	4 (4.5%)	6 (7.0%)	2 (2.3%)	3 (3.8%)	15 (4.4%)
Musculo-skeletal Disorder	**24 (27.9%)**	**27 (30.3%)**	**28 (32.6%)**	**31 (%35.6)**	**28 (33.8%)**	**113 (33.0%)**
Back pain	4 (4.7%)	8 (9.0%)	8 (9.03%)	7 (8.0%)	10 (12.5%)	33 (9.6%)
Arthralgia	4 (4.7%)	7 (7.9%)	6 (7.0%)	5 (5.7%)	10 (12.5%)	28 (8.2%)
Bone fracture	6 (7.0%)	2 (2.2%)	4 (4.7%)	3 (3.4%)	1 (1.3%)	10 (2.9%)

Table 3.13 (cont'd) Number of patients with any adverse event through week 54 by WHOART and preferred term

	Placebo	3 mg/kg q 8 weeks	3 mg/kg q 4 weeks	10 mg/kg q 8 weeks	10 mg/kg q 4 weeks	All Infliximab
Resistance mechanism Disorder	**23 (26.7%)**	**24 (27.0%)**	**33 (38.4%)**	**24 (27.6%)**	**32 (40.0%)**	**113 (33.0%)**
Fever	7 (8.1%)	4 (4.5%)	11 (12.8%)	4 (4.6%)	5 (6.3%)	24 (7.0%)
Moniliasis	1 (1.2%)	4 (4.5%)	6 (7.0%)	2 (2.3%)	8 (10.0%)	20 (5.8%)
Infection	4 (4.7%)	4 (4.5%)	2 (2.3%)	5 (5.7%)	6 (7.5%)	17 (5.0%)
Flu syndrome	3 (3.5%)	5 (5.6%)	3 (3.5%)	3 (3.4%)	4 (5.0%)	15 (4.4%)
Abscess	4 (4.7%)	1 (1.1%)	7 (8.1%)	1 (1.1%)	4 (5.0%)	13 (3.8%)
	Placebo	**3 mg/kg q 8 weeks**	**3 mg/kg q 4 weeks**	**10 mg/kg q 8 weeks**	**10 mg/kg q 4 weeks**	**All Infliximab**
Psychiatric Disorders	10 (11.6%)	15 (16.9%)	14 (16.3%)	15 (17.2%)	11 (13.8%)	55 (16.1%)
Anxiety	4 (4.7%)	4 (4.5%)	5 (5.8%)	5 (5.7%)	4 (5.0%)	18 (5.3%)
Depression	2 (2.3%)	4 (4.5%)	4 (4.7%)	4 (4.6%)	4 (5.0%)	16 (4.7%)
Insomnia	5 (5.8%)	4 (4.5%)	3 (3.5%)	4 (4.6%)	5 (6.3%)	16 (4.7%)
Urinary Disorder	**14 (16.3%)**	**6 (6.7%)**	**12 (14.0%)**	**12 (13.8%)**	**18 (22.5%)**	**48 (14.0%)**
Urinary tract infections	8 (9.3%)	3 (3.4%)	6 (7.0%)	9 (10.3%)	11 (13.8%)	29 (8.5%)
Vascular disorders (noncardiac)	7 (8.1%)	16 (18.0%)	8 (9.3%)	13 (14.9%)	8 (10.0%)	45 (13.2%)
Ecchymosis	0	4 (4.5%)	3 (3.5%)	7 (8.0%)	3 (3.8%)	17 (5.0%)
Flushing	1 (1.2%)	4 (4.5%)	3 (3.5%)	4 (4.6%)	4 (5.0%)	15 (4.4%)
Eye & vision disorders	**2 (2.3%)**	**10 (11.2%)**	**9 (10.5%)**	**14 (16.1%)**	**9 (11.3%)**	**42 (12.3%)**
Conjunctivitis	1 (1.2%)	4 (4.5%)	4 (4.7%)	6 (6.9%)	3 (3.8%)	17 (5.0%)
Vision Abnormal	1 (1.2%)	1 (1.1%)	0	2 (2.3%)	5 (6.3%)	8 (2.3%)
Cardiovascular disorders	**7 (8.1%)**	**10 (11.2%)**	**8 (9.3%)**	**10 (11.5%)**	**12 (15.0%)**	**40 (11.7%)**
Hypertension	5 (5.8%)	6 (6.7%)	5 (5.8%)	8 (9.2%)	8 (10.0%)	27 (7.9%)
Hypotension	2 (2.3%)	2 (2.2%)	2 (2.3%)	2 (2.3%)	4 (5.0%)	10 (2.9%)
Metabolic disorders	**8 (9.3%)**	**8 (9.0%)**	**15 (17.4%)**	**7 (8.0%)**	**9 (11.3%)**	**39 (11.4%)**
Hypokalemia	1 (1.2%)	3 (3.4%)	4 (4.7%)	3 (3.4%)	4 (5.0%)	14 (4.1%)
Weight increase	2 (2.3%)	3 (3.4%)	5 (5.8%)	4 (4.6%)	2 (2.5%)	14 (4.1%)

Through week 54, the body systems for which adverse events were most frequently reported were the respiratory system, gastrointestinal (GI) system, skin, central and peripheral nervous system, body as a whole, musculoskeletal, and resistance mechanism systems. In each of these body systems, more patients treated with infliximab were reported with events compared with patients treated with placebo. Table 3.14 compares the absolute differences between patients treated with infliximab and placebo for these systems at weeks 30 and 54. The differences increased only for skin and resistance mechanism disorders whereas the difference remained the same or decreased for the remaining systems. In other words, with continued exposure to infliximab there was no apparent increased reports of adverse events for the majority of the systems.

Table 3.14 Comparison of the absolute differences between patients treated with infliximab and placebo at weeks 30 and 54.

System	Week 30	Week 54
Respiratory	19.8	14.3
Gastrointestinal	5.2	5.3
Skin	2.0	9.0
Central & peripheral nervous system	12.4	6.9
Whole body	4.5	5.7
Musculoskeletal	9.4	5.1
Resistant Mechanism	4.8	6.3

Over 50% of all infliximab-treated patients experienced an adverse event related to the respiratory and gastrointestinal systems. Respiratory infections were the most common types of adverse event reported. These events included upper respiratory tract infection, sinusitis, coughing, pharyngitis, and rhinitis which were reported in ≥ 5% for each infliximab treatment group. Bronchitis and dyspnea were reported in ≥ 5% for the All Infliximab group.

Gastrointestinal disorders were the second most commonly reported types of adverse events among patients treated with infliximab. The most commonly reported events included nausea, diarrhea, and abdominal pain which occurred with a similar frequency in patients treated with infliximab or placebo. The proportion of patients treated with infliximab and who experienced ulcerative stomatitis and gastroesophageal reflux was higher than patients treated placebo (MTX alone).

Table 3.15 shows the number of patients with one or more adverse event according the individual WHOART preferred term in order of decreasing frequency of events by the total infliximab group, for events that were reported in ≥ 5% of all patients treated with infliximab reported in the week 54 safety update. It should be noted that the follow-up period for the placebo treatment group is less than that for the infliximab treatment group but is close to the follow-up reporting period for the proposed dosing regimen of 3 mg/kg q 8 weeks.

Table 3.15 Number of patients with any adverse event (if in ≥ 5% of all infliximab-treated patients) through week 54.

	Placebo	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks	All Infliximab
Pts treated	86	89	86	87	80	342
Avg weeks follow-up	49.1	51.0	53.8	53.5	53.6	53.0
Pts with ≥ 1 event	81 (94.2%)	82 (92.1%)	79 (91.9%)	85 (97.7%)	78 (97.5%)	324 (94.7%)
URI	19 (22.1%)	35 (39.3%)	23 (26.7%)	33 (37.9%)	24 (30.0%)	115 (33.6%)
Headache	14 (16.3%)	24 (27.0%)	22 (25.6%)	22 (25.3%)	22 (27.5%)	90 (26.3%)
Nausea	18 (20.9%)	17 (19.1%)	16 (18.6%)	17 (19.5%)	15 (18.8%)	65 (19.0%)
Sinusitus	5 (5.8%)	17 (19.1%)	10 (11.6%)	17 (19.5%)	14 (17.5%)	58 (17.0%)
Coughing	6 (7.0%)	10 (11.2%)	9 (10.5%)	17 (19.5%)	14 (17.5%)	50 (14.6%)
Diarrhea	14 (16.3%)	11 (12.4%)	13 (15.1%)	12 (13.8%)	14 (17.5%)	50 (14.6%)
Rash	5 (5.8%)	7 (7.9%)	11 (12.8%)	18 (20.7%)	12 (15.0%)	48 (14.0%)
Fatigue	6 (7.0%)	16 (18.0%)	8 (9.3%)	5 (5.7%)	12 (15.0%)	41 (12.0%)
Pharyngitis	5 (5.8%)	7 (7.9%)	7 (8.1%)	11 (12.6%)	12 (15.0%)	37 (10.8%)
Abdominal pain	8 (9.3%)	7 (7.9%)	12 (14.0%)	10 (11.5%)	8 (10.0%)	37 (10.8%)
Dizziness	10 (11.6%)	8 (9.0%)	8 (9.3%)	14 (16.1%)	7 (8.8%)	37 (10.8%)
Pain	9 (10.5%)	8 (9.0%)	8 (9.3%)	11 (12.6%)	9 (11.3%)	36 (10.5%)
Rhinitis	9 (10.5%)	9 (10.1%)	5 (5.8%)	12 (13.8%)	9 (11.3%)	35 (10.2%)
Back pain	4 (4.7%)	8 (9.0%)	8 (9.3%)	7 (8.0%)	10 (12.5%)	33 (9.6%)
Stomatitis ulcerative	3 (3.5%)	7 (7.9%)	6 (7.0%)	5 (5.7%)	11 (13.8%)	29 (8.5%)
Urinary tract infection	8 (9.3%)	3 (3.4%)	6 (7.0%)	9 (10.3%)	11 (13.8%)	29 (8.5%)
Arthralgia	4 (4.7%)	7 (7.9%)	6 (7.0%)	5 (5.7%)	10 (12.5%)	28 (8.2%)
Hypertension	5 (5.8%)	6 (6.7%)	5 (5.8%)	8 (9.2%)	8 (10.0%)	27 (7.9%)
Dyspepsia	6 (7.0%)	6 (6.7%)	6 (7.0%)	4 (4.6%)	10 (12.5%)	26 (7.6%)
Vomiting	10 (11.6%)	4 (4.5%)	6 (7.0%)	7 (8.0%)	8 (10.0%)	25 (7.3%)
Bronchitis	7 (8.1%)	6 (6.7%)	8 (9.3%)	3 (3.4%)	7 (8.8%)	24 (7.0%)
Fever	7 (8.1%)	4 (4.5%)	11 (12.8%)	4 (4.6%)	5 (6.3%)	24 (7.0%)
Chest pain	6 (7.0%)	5 (5.6%)	5 (5.8%)	7 (8.0%)	6 (7.5%)	23 (6.7%)
Pruritus	0 (0.0%)	5 (5.6%)	8 (9.3%)	4 (4.6%)	5 (6.3%)	22 (6.4%)
Moniliasis	1 (1.2%)	4 (4.5%)	6 (7.0%)	2 (2.3%)	8 (10.0%)	20 (5.8%)
Dyspnea	2 (2.3%)	3 (3.4%)	3 (3.5%)	7 (8.0%)	5 (6.3%)	18 (5.3%)
Anxiety	4 (4.7%)	4 (4.5%)	5 (5.8%)	5 (5.7%)	4 (5.0%)	18 (5.3%)
Infection	4 (4.7%)	4 (4.5%)	2 (2.3%)	5 (5.7%)	6 (7.5%)	17 (5.0%)
Ecchymosis	0 (0.0%)	4 (4.5%)	3 (3.5%)	7 (8.0%)	3 (3.8%)	17 (5.0%)
Conjunctivitis	1 (1.2%)	4 (4.5%)	4 (4.7%)	6 (6.9%)	3 (3.8%)	17 (5.0%)

Adverse Events by treatment cycle

The number of adverse events did not occur more frequently with continued exposure to infliximab over the 30 week period nor with continued follow-up through 54 weeks. Patients treated with placebo had the lowest frequency of adverse events throughout the 30 week period. During the week 2 treatment cycle there was a noticeable increase in the number of patients who had an adverse event in all treatment groups. However, with time the number of events decreased. After the 30 week period, there appears to be less adverse events in patients treated with infliximab, however, the number of patients actually receiving study drug decreased over time resulting in an overall decrease in the frequency of adverse events reported (e.g., at 30 weeks, the total n=356 while at 54 weeks n=304).

Serious Adverse Events

Through week 54, the number of patients treated with placebo (18 of 86; 20.9%) who reported a serious adverse event was higher than those patients treated with infliximab (55 or 342; 16.1%). Because of the diversity of some of these serious adverse events, a limited number of certain adverse events are summarized in Table 3.17. Events that may be associated with serious infections, infusion reactions and malignancies are listed in the table. Because deaths in T22 and preceding clinical trials have included cardiac and thromboembolic events, serious cardiac and vascular events are listed. In addition, patients enrolled into the two clinical trials evaluating infliximab for treatment of Crohn's disease (T16 and T20) experienced acalculous cholecystitis and uretal obstruction as reasonably related serious adverse events, events related to the biliary and urinary tract systems are listed in the table. Inclusion of these events does not imply an association with treatment with infliximab at this time.

Table 3.17 Number of patients with specific serious adverse events through week 54

	Placebo	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks	All Infliximab
Pts treated	86	89	86	87	80	342
Avg weeks follow-up	49.1	51.0	53.8	53.5	53.6	53.0
Pts with ≥ 1 serious event	18 (20.9%)	10 (11.2%)	14 (16.3%)	17 (19.5%)	14 (17.5%)	55 (16.1%)
Musculo-skeletal						
Arthralgia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	1 (1.3%)	2 (0.6%)
Arthritis	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	1 (1.3%)	2 (0.6%)
Respiratory						
Pneumonia	1 (1.2%)	0 (0.0%)	2 (2.3%)	2 (2.3%)	1 (1.3%)	5 (1.5%)
Dyspnea	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	2 (0.6%)
Upper respiratory tract infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	1 (0.3%)
Bronchitis	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Pulmonary infiltrate	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	1 (0.3%)
Gastrointestinal						
Pancreatitis	0 (0.0%)	2 (2.2%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	3 (0.9%)
Resistance Mechanism						
Cellulitis	0 (0.0%)	0 (0.0%)	1 (1.2%)	1 (1.1%)	2 (2.5%)	4 (1.2%)
Sepsis	2 (2.3%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	1 (1.3%)	2 (0.6%)
Herpes zoster	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	2 (0.6%)
Infection bacterial	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Infection fungal	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Infection TBC	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Heart Rate & Rhythm						
Tachycardia	1 (1.2%)	1 (1.1%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	2 (0.6%)
Bradycardia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (0.3%)
Arrhythmia	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	1 (0.3%)
Cardiac arrest	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
AV block complete	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)

Table 3.17 (cont'd.) Number of patients with specific serious adverse events through week 54.

	Placebo	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks	All Infliximab
Vascular (extracardiac)						
Brain infarction	0 (0.0%)	1 (1.1%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	2 (0.6%)
Embolism pulmonary	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Peripheral ischemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (0.3%)
Thrombophletitis deep	1 (1.2%)	1 (1.1%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	2 (0.6%)
Peripheral gangrene	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intestinal ischemia	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hepatic ischemia	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Psychiatric						
Suicide attempt	0 (0.0%)	0 (0.0%)	1 (1.2%)	1 (1.1%)	0 (0.0%)	2 (0.6%)
Liver & Biliary						
Biliary pain	0 (0.0%)	0 (0.0%)	1 (1.2%)	1 (1.1%)	0 (0.0%)	2 (0.6%)
Cholelithiasis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (0.3%)
Hepatic cholestatic	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Myocardial						
Angina pectoris	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (0.3%)
Myocardial ischemia	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Cardiac failure	4 (4.7%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Urinary						
Pyelonephritis	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	1 (1.3%)	2 (0.6%)
Hydronephrosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	1 (0.3%)
Creatinine increased	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Azotemia	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Renal failure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	1 (0.3%)
Urinary retention	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Urinary infection	2 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neoplasms						
Melanoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	1 (0.3%)
Squamous cell	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	1 (0.3%)
Lymphoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	1 (0.3%)
Breast neoplasm	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	1 (0.3%)

One or more of the events listed in Table 3.17 may have been experienced by the same patient. Table 3.18 presents the serious adverse events by patient and separates those that occur before and after week 30.

Table 3.18 Patients in T22 with serious adverse events at week 30 and week 54 by treatment group.

Treatment group	Patient	Before week 30 (verbatim)	After week 30 (preferred term)
Placebo			
	03003	congestive heart failure; chest pain	
	04020		skeletal pain
	06011	Tendon rupture	
	07008	gastric ulcer; erosive gastritis	fever; chills; diabetes; urinary infection
	11005		bone fracture
	12003		urinary tract infection
	12008	pneumonia; cardiac failure; sepsis; intestinal gangrene; respiratory failure	
	13002		knee pain (synovectomy)
	14001	arrhythmia	
	15008	coughing; vomiting; diarrhea; abdominal pain; fever	
	18001	rheumatoid arthritis flare (twice)	
	19012	peripheral gangrene bilateral foot ulcers	skin ulceration
	24005		bone fracture
	27005	urinary retention; sepsis; thrombosis–deep; congestive heart failure	
	30001	ischemic bowel; ischemic liver; cardiopulmonary failure	
	30009	biliary pain (gallstones)	
	31007	bone fracture	
	32006	hyperglycemia; back pain	
	33011	bone fracture; wound infection	
3 mg/kg q 8 wks			
	01008	bronchitis/pneumonia	
	06016	pulmonary emboli (bilateral): DVT	
	14007		pancreatitis
	15001	C-spine disease	
	16006	bone fracture	
	18003	ischemic heart disease; angina pectoris	skin ulceration; vomiting; nausea; herpes zoster; rheumatoid arthritis flare
	18007	Pancreatitis; pancreatic duct stone; weight loss; back pain	weight decrease; back pain
	19005	orthopnea; paroxysmal nocturnal dyspnea; tachycardia	dyspnea, AV block complete
	28002		rheumatoid arthritis
	33015	CVA	

Table 3.18 (cont'd.) Patients in T22 with serious adverse events at week 30 and week 54 by treatment group.

Treatment group	Patient	Before week 30 (verbatim)	After week 30 (preferred term)
3 mg/kg q 4 wks			
	06009	ruptured tendon	biliary pain; diaphragmatic hernia
	06017	rheumatoid arthritis flare	
	10004	anxiety w/suicidal overtones; dehydration w/delirium; tachycardia; creatinine increased; azotemia	
	11006	pneumonia	
	16004	cerumen obstruction of both ears	
	18002	weight loss; cough; abdominal pain; vomiting; night sweats; pneumonia; rheumatoid flare; lymphadenopathy	infection bacterial; infection tubercular; pulmonary edema; resp insufficiency; pneumothorax; abdominal pain; pleural effusion; encephalopathy; hepatitis; cardiac arrest
	20007	DVT; hemarthrosis	bone fracture
	21003	gastrointestinal ulcer; pancreatitis; dehydration	
	21013	microcytic anemia	
	24007	pyelonephritis	
	26009		syncope; nausea
	28001	bacteremia; septic arthritis; spinal cord lesion; respiratory insufficiency	
	30007		brain infarction
	32005		cellulitis
10 mg/kg q 8 wks			
	01006		peripheral ischemia
	02002		cholelithiasis; biliary pain
	02006		appendicitis
	04009		angina; chest pain; bradycardia
	08004	bone fracture; leg pain	
	08010		endometriosis
	12005		arthralgia; joint cyst
	12006	osteoarthritis-cystic	
	14002	pneumonia	
	15009	cellulitis; lymphangitis	
	18009		inflammation
	20009	suicide attempt	
	22001		anemia; thinking abnormal; peritonitis; coccidioidomycosis
	28004	Herpes zoster	
	29001		GI hemorrhage
	30003	dyspnea	
	31005	pneumonia; leukopenia	

Table 3.18 (cont'd.) Patients in T22 with serious adverse events at week 30 and week 54 by treatment group.

Treatment group	Patient	Before week 30 (verbatim)	After week 30 (preferred term)
10 mg/kg q 4 wks			
	04018	rupture tendons	
	05012	pyelonephritis; confusion; anemia; lung infiltrate; renal failure; hydronephrosis; cellulitis; lymphoma	pyelonephritis; lymphoma; cellulitis; arrythmia
	07006	intervertebral disk rupture	
	09008		pneumonia
	10009	bone pain	
	11011	sepsis	
	12002	coxitis aseptic	
	12007		upper respiratory tract infection
	15016	cellulitis; cracked skin	
	16002		abdominal pain
	17016	tendon rupture	
	25009		symphysiolysis; spondylotisthesis; osteoarthritis
	27003	breast neoplasm	back pain
	27008	squamous cell carcinoma; melanoma	melanoma

Adverse events that resulted in discontinuation from T22

Patients were considered to have discontinued treatment if they did not receive all of the infusions in their prescribed treatment regimen or if they received only a partial, last infusion. The proportion of patients who discontinued treatment due to an adverse event by week 54 in any treatment groups was similar (Table 3.20). At week 30, there were almost twice as many placebo-treated patients (8.1%) compared to patients treated with infliximab (4.7%) who had discontinued study treatment due to adverse events. Table 3.20 also lists the serious adverse events associated with discontinuations. Dyspnea and sepsis caused the discontinuation for two patients, each, treated with infliximab. Cardiac failure resulted in discontinuation of study drug for 2 patients treated with placebo and for none of the patients treated with infliximab. Three patients with serious adverse event discontinued treatment due to infusion reactions; two patients experienced dyspnea and one patient experienced hypotension.

Table 3.20 Number of patients who discontinued treatment due to adverse event by week 54 and type of adverse event reported (WHOART) for each patient discontinued in treatment group*

	Placebo	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks
Pts treated	86	89	86	87	80
Avg weeks follow-up	49.1	51.0	53.8	53.5	53.6
Pts who discontinued	7 (8.1%)	5 (5.6%)	8 (9.3%)	4 (4.6%)	8 (10.0%)
Event per patient					
	33011- bone fracture	18003 - skin ulceration	25004 - urticaria	08004-bone fracture	dermatitis
	32006-hyperglycemia	25010 – dyspnea	04013-dyspnea	18005-lupus syndrome	15016-cracking of skin
	19012-peripheral gangrene	14007 – pancreatitis	bursitis	20009-suicide attempt	07006-vertebral disk herniation
	30001-CHF	06016 - PE	28001 - sepsis	02002-abnormal liver function	11011 - sepsis
	03005-CHF	08005 -hot flushes	32005-cellulitis		05012 – pyelonephritis; renal failure
	01016-Anemia		24007-pyelonephritis		27008 - melanoma
	07004-thrombo-cytopenia		01009-hyperglycemia		27003 - breast cancer
			24004-hypotension		19014-palpitation

*Patient identifiers could not be determined from review of the summary of safety data at 54 weeks for two adverse events resulting in discontinuation.

3.3.3.2 Deaths in T22

Through week 54, 8 patients died. Five patients died during the first 30 weeks of the clinical trial period. Five patients received infliximab; one patient from each dosing regimen died with the additional patient from the 3 mg/kg q 4 week regimen. The immediate most probable causes of death identified by the investigators were intestinal gangrene, arrhythmia, and cardiac failure in the placebo-treated patients and pulmonary embolisms, cardiopulmonary failure, disseminated tuberculosis, coccidioidomycosis, and cardiac failure in the infliximab-treated patients.

A descriptive narrative of the deaths in these 8 patients (12008, 14001, 30001, 06016, 28001, 18002, 22001, 05012) in T22 are provided in the review of the consolidated safety database (Section 4.0)

3.3.3.3 Malignancies in T22

Through week 54, 5 patients were reported with neoplasms but only 4 had malignancy; the fifth patient had a benign uterine polyp before week 30. Three of the 4 patients were diagnosed with malignancy prior to week 30 and the 4th patient was diagnosed with basal cell carcinoma after week 30 but this event was present at study entry and was considered ongoing. The three newly diagnosed malignancies occurred in patients treated with 10 mg/kg q 4 weeks and included large cell lymphoma, recurrent breast adenocarcinoma (initial incidence, 9 years prior), and squamous cell and melanoma (both skin cancers occurred in one patient). The fourth patient with basal cell carcinoma was treated with infliximab at a dose of 10mg/kg q 8 weeks.

A descriptive narrative of each patient who developed malignancy in T22 (05012, 27003, 27008, 25007) is provided in the review of the consolidated safety database.

3.3.3.4 Infusion Reactions in T22

An infusion reaction was defined as any adverse event that occurred during an infusion or within 1 hours following the end of that infusion, or was judged by the investigator to be an infusion reaction. Although administering medicines (acetaminophen, Benadryl) prior to the infusion of study drug was not a protocol violation, principal investigators were encouraged not to do so. However, there were 43 (10%) of all patients who received prophylactic medicines prior to any study drug infusion (Table 3.21). Consequently, the incidence of infusion reactions reported in this section may be lower.

All 11 patients at site 11 received prophylactic medicines with each infusion; 13 of the 15 patients enrolled at site 1 received prophylactic medicines prior to most, but not all infusions. Most of the remaining patients received sporadic prophylactic medicines for infusion reactions. It is noteworthy that none of the patients enrolled at site 11 responded clinically to treatment with infliximab; 4 of the 11 patients at site 1 who were administered infliximab responded to treatment.

Table 3.21 Patients who received prophylaxis

Patient/Dose group	Infusion Number w/IRP[a]	Infusion Number where Pt had reaction	Time if Discontinued	Response[b]
Placebo (n=6)				
01001	1-2-3-4			NR
01010	All 2		Wk 6	NR
01013	4-6-8			NR
11005	All 9			NR
11007	All 8			NR
15015	2-3-4-5-6			NR
3 mg/kg q 8 week (n=8)				
01008	All 5		Wk 14	NR
01014	1-5			NR
09002	1-2-3			NR
11001	All 6	1-2	Wk 18	NR
11009	All			NR
15007	6-7-8	5		NR
30002	7	5	Wk 22	NR
33003	8	1-5-6-8		R
3 mg/kg q 4 weeks (n=9)				
01003	All 8			NR
01009	All 6		Wk 18	NR
01015	All 8			NR
04013	8-9	6-7		NR
09004	1-2-3-5			NR
11004	All 8	1-2-3		NR
11006	All 8			NR
30007	6-7-8-9	4-5-6-7		NR
33012	4-9	3-4-8		NR

Table 3.21 (cont'd) Patients who received prophylaxis

Patient/Dose group	Infusion Number w/IRP[a]	Infusion Number where Pt had reaction	Time if Discontinued	Response[b]
10 mg/kg q 8 wks (n=12)				
01005	1-2-3-4-5-6-7			NR
01006	1-2			NR
01011	1-2-3-4-5-6-7			R
04009	5-6			R
05021	7-8			NR
09007	1			R
11002	All 8	3-7		NR
11010	All 8			NR
14002	4-5-6-7-8	1-2		R
29001	1-2			NR
32003	8	1		NR
33013	7-8	2-3-4		R
10 mg/kg q 4 wks (n=8)				
01004	All 8			R
01007	1-2-5-6-8			R
01012	1-2-3-4-5-6			R
04008	4			R
11003	All 8	1-2-8		NR
11008	All 3		Wk 6	NR
11011	All 3		Wk 6	NR
32002	2-3-5-6-7-8	1		NR

[a] IRP – infusion reaction prophylaxis

[b] R=responder; NR=nonresponder

Note: all patients at site 11 received prophylaxis and all but patients 01002 and 01016 at site 1 received prophylaxis.

Table 3.22 summarizes the number of patients who had an infusion reaction through weeks 30 and through weeks 54. The incidence of infusion reactions was higher for infliximab-treated patients than for placebo-treated patients at both time points and the overall treatment effect at week 54 remained not statistically significant. (For all of the following tables, patients in the every 8 week groups are counted only by reactions reported with the infliximab (not placebo) infusions.)

Table 3.22 Incidence of infusion reactions at week 30 and 54.

	Placebo	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks	All Infliximab	Treatment effect p-value
Pts treated	86	89	86	87	80	342	
Through week 30							
Avg number of infusions	6	5	8	5	8	6	
Infusions with reactions	12 (2.2%)	19 (4.5%)	36 (5.5%)	24 (5.6%)	21 (3.5%)	100 (4.8%)	
Pts with ≥ 1 infusion reaction	9 (10.5%)	14 (15.7%)	16 (18.6%)	16 (18.4%)	16 (20.0%)	62 (18.1%)	0.48
Through week 54							
Avg number of infusions	10	8	13	8	13	10	
Infusions with reactions	16 (1.8%)	21 (3.0%)	53 (4.7%)	37 (5.1%)	26 (2.5%)	137 (3.8%)	
Pts with ≥ 1 infusion reaction	9 (10.5%)	16 (18.0%)	20 (23.3%)	20 (23.0%)	17 (21.3%)	73 (21.3%)	0.18

The types of adverse events through week 54 that were associated with infusion reactions were grouped as nonspecific, dermatological, those related to the cardiopulmonary system, and those related to the injection site. Nonspecific adverse events included headache, nausea, fever, fatigue chills, increased sweating, abdominal pain, paresthesia, etc. Dermatological events included pruritus, urticaria, flushing, rash, erythema, skin discoloration, and folliculitis. Cardiopulmonary included hypertension, dizziness, hypotension, dyspnea, chest pain, hot flushes, tachycardia, vertigo, arrhythmia, and cyanosis. Injection related events include injection site inflammation, pain, and infiltration. Table 3.23 summarizes the adverse event related to infusion reactions according to these four categories. The incidence of these categorized events was higher in patients treated with infliximab with the most frequent infusion related events occurring in the 3 mg/kg q 4 weeks cohort.

Table 3.23 Number of categorized adverse events associated with study drug infusion through week 54

	Placebo	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks
Pts treated	86	89	86	87	80
Avg number of infusions	10	8	13	8	13
Infusions with reactions	16 (1.8%)	21 (3.0%)	53 (4.7%)	37 (5.1%)	26 (2.5%)
Pts with ≥ 1 infusion reaction	9 (10.5%)	16 (18.0%)	20 (23.3%)	20 (23.0%)	17 (21.3%)
Category					
Cardiopulmonary	4 (4.7%)	10 (11.2%)	13 (15.1%)	11 (12.6%)	10 (12.5%)
Dermatological	1 (1.2%)	5 (5.6%)	12 (14.0%)	4 (4.6%)	4 (5.0%)
Nonspecific	7 (8.1%)	9 (10.1%)	28 (32.6%)	17 (19.5%)	12 (15.0%)
Injection related	1 (1.2%)	2 (2.3%)	3 (3.5%)	1 (1.2%)	1 (1.3%)

Adverse events potentially associated with immediate hypersensitivity reactions include hypotension, dyspnea, and hives. There were no reports of hives associated with study drug infusion for any of the treatment groups. Table 3.24 lists the incidence of these reactions and includes facial and periorbital edema for completeness.

Table 3.24 Incidence of hypotension, dyspnea, and facial and periorbital edema.

	Placebo	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks	All Infliximab
Pts treated	86	89	86	87	80	342
Avg number of infusions	10	8	13	8	13	10
Infusions with reactions	16 (1.8%)	21 (3.0%)	53 (4.7%)	37 (5.1%)	26 (2.5%)	137 (3.8%)
Pts with ≥ 1 infusion reaction	9 (10.5%)	16 (18.0%)	20 (23.3%)	20 (23.0%)	17 (21.3%)	73 (21.3%)
Hypotension	2 (2.3%)	2 (2.2%)	2 (2.3%)	1 (1.1%)	4 (5.0%)	9 (2.6%)
Dyspnea	0 (0.0%)	1 (1.1%)	3 (3.5%)	0 (0.0%)	0 (0.0%)	4 (1.2%)
Facial/periorbital edema	0 (0.0%)	0 (0.0%)	2 (2.3%)	0 (0.0%)	0 (0.0%)	2 (0.6%)

There were no serious infusion reactions reported through week 54. However, two patients had infusion reactions that were considered by the investigator to be severe; both occurred prior to week 30.

- Patient 25004 (3 mg/kg q 4 wks), a 60-year old female with a 15-year history of rheumatoid arthritis, had previously had mild pruritus during the fourth infusion which resolved within 0.4 hours with Benadryl. However, the patient developed severe urticaria within 10 minutes of the start of the fifth infusion. The infusion was discontinued after 25 minutes, and Benadryl and Celestone IM were administered, with resolution of the urticaria approximately 1 hour after the end of the infusion. The principal investigator considered the urticaria related to study medication and the patient was discontinued from further study treatment.

- Patient 30007 (3 mg/kg q 4 wks) was reported with a series of vasodilatory type of infusion reactions including flushing, headache, nausea, and vomiting associated with infusions 4 through 8. During infusions 4 through 6, the events occurred within 10 to 20 minutes of the start of infusion, were considered moderate, and resolved within 20 minutes with a change in infusion rate. During the seventh infusion, the patient experienced flushing, headache, and vomiting which were considered severe, occurred within 5 minutes of infusion start, and resolved within 20 minutes without treatment or change in infusion. During the eighth infusion, severe flushing, nausea, hot flushes, increased sweating and vomiting occurred within 15 minutes of infusion start, and also resolved within 20 minutes without treatment or change in infusion. All events were considered related to study agent and the patient received all scheduled study infusions.

Data on infusion reactions by treatment group and baseline MTX are available through week 30 and are summarized in Table 3.25. There is a suggestion that for each infliximab treatment groups, patients treated with >20 mg/week of MTX experienced less infusion reactions compared to patients who received lower doses of MTX except for the group with the highest infliximab exposure, 10 mg/kg q 4 weeks.

Table 3.25 Number of patients with any infusion reaction to week 30 by baseline MTX dose.

	Placebo	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks
Pts treated	86	89	86	87	80
Avg number of infusions	6	5	8	5	8
Pts with ≥ 1 infusion reaction	9 (10.5%)	14 (15.7%)	16 (18.6%)	16 (18.4%)	16 (20.0%)
Patients with ≥ 1 reaction by MTX dose					
≤ 12.5 mg/week					
Pts treated	24	28	26	24	18
Pts w/≥ 1 reaction	2 (8.3%)	5 (17.9%)	5 (19.2%)	5 (20.8%)	3 (16.7%)
>12.5 and <20 mg/week					
Pts treated	44	40	40	45	40
Pts w/≥ 1 reaction	5 (11.4%)	7 (17.5%)	8 (20.0%)	9 (20.0%)	9 (22.5%)
≥ 20 mg/week					
Pts treated	18	21	20	18	22
Pts w/ ≥ 1 reaction	2 (11.1%)	2 (9.5%)	3 (15.0%)	2 (11.1%)	4 (18.2%)

3.3.3.5 Infections

Treated Infections

Adverse events were considered to be infections if the investigator recorded the event as such on the CRF or if the patient was treated with an oral or parenteral antibiotic within 1 week of the adverse event. The number of patients with infection treated with an antimicrobial in ≥ 2 patients treated with infliximab is summarized in Table 3.27. Through week 54, 149 (43.6%) of the 342 patients treated with infliximab and 30 of the 86 (34.9%) of patients treated with placebo were treated with an antibiotic for an infection. Through week 20, 106 (31.0%) of the 342 patients treated with infliximab and 18 of the 86 (20.9%) of patients treated with placebo were treated with an antibiotic for an infection.

Upper respiratory tract infection, sinusitis, urinary tract infection (URI), pharyngitis, bronchitis, infection, moniliasis, pneumonia, and abscess were the most commonly treated infections in patients treated with infliximab. Upper respiratory tract infection, bronchitis, URI, and abscess were the most commonly treated infections in patients treated with placebo.

Table 3.26 Number of patients with infections treated with antimicrobials that occurred in ≥ 2 patients treated with infliximab through week 54.

	Placebo	3 mg/kg q 8 weeks	3 mg/kg q 4 weeks	10 mg/kg q 8 weeks	10 mg/kg q 4 weeks
Pts treated	86	88	86	87	81
Avg weeks follow-up	49.1	51.6	53.7	54.1	53.3
Pts with ≥ 1 serious infection	30 (34.9%)	30 (34.1%)	35 (40.7%)	46 (52.9%)	38 (46.9%)
Event in ≥ 2 infliximab-treated patients					
Upper respiratory tract	7 (8.1%)	9 (10.2%)	8 (9.3%)	7 (8.0%)	7 (8.6%)
Sinusitus	2 (2.3%)	6 (6.8%)	3 (3.5%)	9 (10.3%)	8 (9.9%)
Urinary tract infection	5 (5.8%)	3 (3.4%)	4 (4.7%)	9 (10.3%)	8 (9.9%)
Pharyngitis	0 (0.0%)	1 (1.1%)	5 (5.8%)	6 (6.9%)	5 (6.2%)
Infection	2 (2.3%)	2 (2.3%)	1 (1.2%)	5 (5.7%)	7 (8.6%)
Bronchitis	6 (7.0%)	2 (2.3%)	4 (4.7%)	3 (3.4%)	6 (7.4%)
Moniliasis	0 (0.0%)	1 (1.1%)	4 (4.7%)	1 (1.1%)	3 (3.7%)
Pneumonia	1 (1.2%)	0 (0.0%)	4 (4.7%)	2 (2.3%)	2 (2.5%)

Table 3.26 (cont'd.) Number of patients with infections treated with antimicrobials that occurred in ≥ 2 patients treated with infliximab through week 54.

	Placebo	3 mg/kg q 8 weeks	3 mg/kg q 4 weeks	10 mg/kg q 8 weeks	10 mg/kg q 4 weeks
Abscess	4 (4.7%)	0 (0.0%)	4 (4.7%)	0 (0.0%)	3 (3.7%)
Cellulitis	0 (0.0%)	2 (2.3%)	1 (1.2%)	2 (2.3%)	2 (2.5%)
Cystitis	0 (0.0%)	0 (0.0%)	3 (3.5%)	2 (2.3%)	1 (1.2%)
Otitis	0 (0.0%)	2 (2.3%)	2 (2.3%)	1 (1.1%)	1 (1.2%)
Coughing	0 (0.0%)	0 (0.0%)	1 (1.2%)	2 (2.3%)	2 (2.5%)
Infection bacterial	1 (1.2%)	0 (0.0%)	2 (2.3%)	2 (2.3%)	1 (1.2%)
Herpes zoster	1 (1.2%)	1 (1.1%)	1 (1.2%)	2 (2.3%)	1 (1.2%)
Dermatitis	0 (0.0%)	0 (0.0%)	3 (3.5%)	0 (0.0%)	1 (1.2%)
Stomatitis ulcerative	0 (0.0%)	1 (1.1%)	1 (1.2%)	1 (1.1%)	0 (0.0%)
Fever	0 (0.0%)	1 (1.1%)	1 (1.2%)	0 (0.0%)	1 (1.2%)
Infection fungal	0 (0.0%)	0 (0.0%)	3 (3.5%)	0 (0.0%)	0 (0.0%)
Sepsis	1 (1.2%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	2 (2.5%)
Bursitis	0 (0.0%)	0 (0.0%)	1 (1.2%)	2 (2.3%)	0 (0.0%)
Diarrhea	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	1 (1.2%)
Gastroenteritis	0 (0.0%)	1 (1.1%)	1 (1.2%)	0 (0.0%)	0 (0.0%)
Dysuria	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	1 (1.2%)
Pyelonephritis	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	1 (1.2%)
Influenza-like symptoms	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (1.1%)	0 (0.0%)
Chills	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
Influenza	0 (0.0%)	1 (1.1%)	1 (1.2%)	0 (0.0%)	0 (0.0%)
Flu syndrome	0 (0.0%)	0 (0.0%)	1 (1.2%)	1 (1.1%)	0 (0.0%)
Furuncle	1 (1.2%)	1 (1.1%)	1 (1.2%)	0 (0.0%)	0 (0.0%)

Serious infections

The sponsor updated the week 54 summary safety data regarding infections later during the review process so the data presented in the review is complete through the 54 week period for all of the patients enrolled into T22. Unlike the previous update, the clinical data analyzed for infections through 54 was the unblinded data. For these analyses, patient 33015, who had been randomized to the 10 mg/kg q 4 weeks cohort but treated similar to the 3 mg/kg q 8 weeks for the initial part of the study, is included in the 10 mg/kg q 4 weeks cohort since he was treated appropriately during the post week 30 period. The two patients randomized to placebo but received 0.5 mg/kg infliximab for one dose remain in the 3 mg/kg q 8 weeks cohort for these safety analyses.

A list the patients with serious infections at the various timepoints during the conduct of T22, i.e., by week 30, week 54 and subsequent to week 54 is provided in Appendix 3.C. Narratives for these infections are provided in the review of the consolidated safety database.

Through week 54, 20 of 342 (5.8%) patients treated with infliximab and 7 of 86 (8.1%) patients treated with placebo experienced a serious infection. Through week 30, 14 patients (7.0%) patients treated with infliximab and 5 (5.8%) patients treated with placebo had a serious infection. Serious infections that were reported in more than 1 patients treated with infliximab were pneumonia, cellulitis, pyelonephritis, sepsis, and herpes zoster (Table 3.26). At 54 weeks, the 3 mg/kg q 8 week dosing group had the least number of serious infections while the number of patients with serious infections for the remaining three dosing groups were comparable.

Table 3.27 Patients with serious infections that occurred in ≥ 2 patients treated with infliximab through week 54.

	Placebo	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks
Pts treated	86	88	86	87	81
Avg weeks follow-up	49.1	51.6	53.7	54.1	53.3
Pts with ≥ 1 serious infections	7 (8.1%)	2 (2.3%)	6 (7.0%)	7 (8.0%)	6 (6.2%)
Event in ≥ 2 infliximab-treated patients					
Pneumonia	1 (1.2%)	0 (0.0%)	2 (2.3%)	2 (2.3%)	1 (1.2%)
Cellulitis	0 (0.0%)	0 (0.0%)	1 (1.2%)	1 (1.1%)	1 (1.2%)
Pyelonephritis	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	1 (1.2%)
Infection bacterial	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	1 (1.2%)
Sepsis	2 (2.3%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	1 (1.2%)
Herpes zoster	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (1.1%)	0 (0.0%)

Clinically Noteworthy Infections

In an attempt to characterize better the events related to infections, both serious and non-serious, the sponsor conducted another analysis where they differentiated infections into clinically noteworthy and not clinically noteworthy based upon a blinded review of adverse events coded as infections in the week 54 database. Events in the clinically noteworthy category included principally bacterial infections such as sepsis, pneumonia, and abscess, i.e., infections that are likely to be treated with an antimicrobial agent and that, if left untreated, could have medically significant sequellae.

The incidence of infections that were clinically noteworthy occurred in 14% to 26% of the patients and were higher in patients treated with infliximab compared to placebo. There also appeared to be a dose-responsive relationship between dose and incidence of noteworthy infections with 15.9% in the 3 mg/kg q 8 weeks group to 25.9% in the 10 mg/kg q 4 weeks group, compared to 14.0% in placebo. In contrast to infections that were not clinically noteworthy, the infections designated by the sponsor as clinically noteworthy generally lasted longer in patients treated with infliximab than in patients treated with placebo (median duration approximately twice as long). Only a small proportion of patients (2-6%) of these noteworthy infections were serious (i.e., required prolong hospitalization) and the duration of serious infections was only slightly longer in the infliximab groups compared to placebo.

3.3.3.6 Autoimmune antibodies and syndromes

The review of autoimmune antibodies includes only data through week 30. No analyses of the week 54 data have been submitted.

Antinuclear Antibodies (ANA).

Serum samples obtained prior to infusion at weeks 0, 2, 6, 10, 18 , and 26 were tested for ANA using Hep-2 cells with a starting dilution of 1:40. The data on the 1:40 cut-off were reviewed. A cut-off of 1:320 was accepted as more clinically meaningful because of the high background level and variability with the 1:40 cut-off. In addition, [redacted] the central laboratory that assayed the samples, considered results ≥ 1:320 to be clinically significant for this assay in their laboratory.

If positive for ANA, the samples were tested for anti-dsDNA. Both an immunofluorescence technique (IFT) on C*rithidia luciliae* and the FARR method were used to test anti-dsDNA. A sample was considered positive for anti-dsDNA antibodies if it tested positive by both the *Crithidia* (IgG) and FARR methods. The FARR assay was performed to confirm the Crithidia test results because this assay provides a quantitative assessment and only detects high avidity/affinity antibodies which are thought to be clinically

relevant in systemic lupus erythematous (SLE)). Samples positive for ANA at 1:320 were considered to be clinically significant by the FARR method if results were >25 IU/ml.

Change from baseline ANA through week 30 using the ≥ 1:320 cut-off are shown in Table 3.28. Overall, 80 of the 341 evaluated patients (23.5%) in all infliximab treatment groups and 5 of the 84 patients (6.0%) patients treated with placebo developed new ANAs. The proportion of evaluated patients with newly positive ANA results in each of the infliximab treatment groups ranged from 15.0% (12/80) in the 10 mg/kg q 4 weeks group to 27.0% (24/89) in the 3 mg/kg q 8 weeks group. There were 273 patients treated with infliximab and 69 patients treated with placebo who were negative for ANA at baseline. Eighty (29.3%) of the infliximab-treated patients and 5 (7.2%) of placebo-treated patients became positive in at least 1 follow-up sample (overall treatment effect p-value <0.001), with 70 (25,6%) infliximab-treated patients and 2 (2.9%) placebo-treated patients positive at the last evaluation. The number of patients with negative results at baseline who became positive for ANA at any time was greater ($p < 0.001$) than that in the placebo cohort in each of the infliximab treatment groups except the 10 mg/kg q 4 weeks group ($p=0.07$). There was no apparent treatment-dependent effect with respect to the incidence of patients who became positive for ANA.

Conversely, there were 68 infliximab-treated patients who were positive for ANA at baseline. Twenty-three (33.8%) were negative at any time after the baseline evaluation and 13 (19.1%) were negative at the last evaluation. Of the 15 patients treated with placebo who were positive for ANA at baseline, 2 (13.3%) were negative at any time after the baseline evaluation and 1 (6.7%) was negative at the last evaluation. The proportion of patients treated with infliximab who converted from positive to negative was approximately 3 times greater for each of the infliximab treatment groups compared to placebo, except the 3 mg/kg q 4 weeks group where approximately twice the number converted from positive to negative.

Table 3.28 Change from baseline in ANA results through week 30 (Cut-off criteria of ≥ 1:320).

	Placebo	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks
Pts treated	86	89	86	87	80
Pts evaluated	84	89	85	87	80
ANA neg at baseline	69	75	64	71	63
(+) at any time	5	24	21	23	12
p-value vs. placebo		<0.001	<0.001	<0.001	0.07
(+) at last evaluation	2	20	19	19	12
(-) throughout 30 wks	64	51	43	48	51
ANA pos at baseline	15	14	21	16	17
(-) at any time	2	6	4	6	7
(-) at last evaluation	1	4	3	3	3
(+) throughout 30 wks	13	8	17	10	10

Anti-double stranded DNA (anti-dsDNA) antibodies.

The changes from baseline in anti-dsDNA antibody results through week 30 using ≥ 1:320 ANA cut-off are summarized in Table 3.29. None of the patients treated with placebo had positive anti-dsDNA antibody results (FARR >25 IU/ml). Of the 341 evaluated infliximab-treated patients, 15 (4.4%) had newly positive anti-dsDNA antibody results (overall treatment effect p-value =0.2) and 13 of 341 (3.8%) had positive results at their last evaluation. At the last evaluation, 13 (5.2%) of 252 evaluable infliximab-treated patients were positive for anti-dsDNA antibody compared to none of the placebo-treated patients. The proportion of evaluated patients with newly positive anti-dsDNA antibody results in each of the infliximab treatment groups ranged from 2.5% (2/80) in the 10 mg/kg q 4 weeks group to 5.9% (5/85) in the 3 mg/kg q 4 weeks group. There was no apparent treatment dependent effect associated with the incidence of patients with newly positive anti-dsDNA antibodies.

Table 3.29 Change from baseline in anti-dsDNA antibody results through week 30 using a ≥ 1:320 ANA cut-off and a >25 IU/ml FARR result.

	Placebo	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks
Pts treated	86	89	86	87	80
Pts evaluated	84	89	85	87	80
anti-dsDNA neg at baseline	84	89	85	87	80
(+) at any time	0	3	5	5	2
(+) at last evaluation	0	3	4	4	2
(-) through week 30	84	86	80	82	78

Autoimmune Disorders.

There have been 2 patients in previous trials who were treated with infliximab and who developed an autoimmune disorder (see Review of the consolidated safety database). One patient had rheumatoid arthritis while the other patient had received infliximab in a clinical trial evaluating the efficacy of infliximab for treatment of Crohn's disease. In T22, 1 of 342 patients treated with infliximab developed a lupus-like syndrome. A brief description of this patient follows.

- Patient 18005 was a 48-year-old female with an 18-year history of RA treated with MTX, and was randomized to receive infliximab 10 mg/kg q 8 wks. Approximately 2 weeks after receiving the second (week 2) infusion, the patient developed a persistent rash on the hands and forearms, and a biopsy showed mild perivascular inflammatory infiltrate suggestive of drug reaction. An immunology screen performed approximately 2 months later was ANA-negative, showed low complement (C4), and was positive for cardiolipin antibodies. The rash on hands and forearms

was treated and was considered resolved approximately 3 months after onset. One month later, the patient developed itchy spots on forearms, erythema on both cheeks, and puffiness around eyes, and a second immunology screen showed anticardiolipin antibodies, low C4, weakly positive ANA, and negative anti-dsDNA. A diagnosis of drug-induced lupus erythematosus was made based upon the results of this immunology screen, as well as a butterfly pattern facial skin rash in combination with the rash on forearms. The erythema on both cheeks was treated with hydrocortisone cream and was considered ongoing beyond week 30. The principal investigator considered the lupus as probably related to study agent. The patient did not receive any additional study agent infusions beyond week 2 due to the rash.

Human Antichimeric Antibodies (HACA).

Patients who discontinued study treatment.

HACA was not analyzed for all patients due to the ongoing treatments in the study; Circulating concentrations of infliximab can interfere with the detection of induced immune reactions. HACA was analyzed for the patients who discontinued study treatment through week 30. Of the 342 infliximab-treated patients, there were 52 who discontinued treatment by week 30. HACA samples were available on 32 of these patients. Seven of these 32 patients had inconclusive HACAs because of detectable infliximab concentrations. Of the remaining 25 patients, HACA was detected in only 1 patient and the remaining 25 patients were HACA negative. The HACA-positive patient had a titer of 1:10 observed at 28 weeks. The patients had received 3 mg/kg q 8 weeks for a total of 8 infusions of study drug (5 infusions of infliximab and 3 infusions of placebo). The patient discontinued due to lack of efficacy and did not experience any serious adverse events.

Approximately 63% of the HACA-negative, infliximab-treated patients discontinued treatment by week 30 due to lack of efficacy and 33% discontinued for safety reasons. Of the 7 patients with inconclusive HACA status, 71% discontinued due to lack of efficacy and 29% discontinued due to safety reasons. The proportions are comparable to the placebo-treated patients who discontinued. Of the 20 placebo-treated patients 65% discontinued due to lack of efficacy and 25% discontinued for safety reasons.

The single HACA-positive patient did not have an infusion reaction following any of the 8 infusions. The 24 HACA-negative infliximab-treated patients received a total of 120 infusions of either infliximab or placebo. A total of 8 infusions in 5 HACA-negative patients were associated with an infusion reaction. Three of the 5 patients were in the 3 mg/kg q 8 week group and the remaining 2 patients were in different treatment groups. Two of the 7 infliximab-treated patients for whom the HACA status is inconclusive experienced infusion reactions. These results are higher than observed for the placebo-group, in which no patient had an infusion reaction.

Patients who did not receive study drug for ≥ 8 weeks between year 1 and year 2.

HACA analyses were also performed by the sponsor in a blinded fashion in a subset of patients who completed a full year (54 weeks) of treatment and had an interval ≥ 8 weeks prior to retreatment in the second year. The clinical data is only unblinded through week 54 and there may be some additional patients who fulfill this definition. In addition, it was difficult to select which samples corresponded to the most appropriate time periods for HACA analyses, since the final treatment time periods were unknown. Therefore, these results should be regarded as preliminary.

Of the 342 patients treated with infliximab, there were 84 patients known to have at least an 8 week interval between the 1st and 2nd years of the study. Seventy-six patients had samples available for HACA analysis: HACA was detected in 2 patients, 31 patients were HACA negative, and 43 had inconclusive HACA status due to detectable serum infliximab concentrations.

The titers for the two positive patients were 1:320 and 1:40, four weeks after their last infusion. Samples were obtained at 4 weeks after the last infusion since this was the original sampling schedule per protocol (i.e., at 4, 8, 12, and 20 weeks after week 54). These 2 patients received 3 mg/kg q 4 weeks and q 8 weeks, respectively. Patient 08002 who had the 1:40 titer, had no infusion reaction. Patient 05004 had the 1:320 titer, and had moderate urticaria starting 40 minutes after the beginning of the week 30 infusion. The reaction was not serious but definitely related to study drug. The infusion was completed after a 20 minute pause and the patient was treated with antihistamines for the urticaria which resolved after 20 minutes. The patient received subsequent infusions uneventfully. By 20 weeks after the last infusion and prior to retreatment, the HACA titers for these 2 patients had decreased from 1:40 to 0, and from 1:320 to 1:80.

3.3.3.7 Laboratory Test Results

The tabulated laboratory results for through week 30 and the summary of the laboratory results through week 54 were reviewed. Because two of the major side effects of MTX include liver toxicity and neutropenia, only the hematology and chemistries evaluating liver function are presented in this review.

Clinically significant changes in laboratory results were defined for baseline values within the normal range, outside the normal range and for those instances where no values were available. For a baseline value within the normal range, change was defined as a post-treatment value outside the normal range and a change of at least 25% from baseline. For a baseline value outside the normal range, change was defined as a change in a post-treatment value of at least 25% in the same direction or a value outside the normal range in the opposite direction. If no baseline value was available, a change was defined as a post-treatment value outside the normal range.

Hematology.

Table 3.30 summarizes the number of patients with clinically noteworthy changes in platelets, total WBC counts, neutrophils, lymphocytes and monocytes. Through week 54, 2 patients who received infliximab had decreases in both hemoglobin and hematocrit; and 2 patients each who received placebo had a decrease in hemoglobin and hematocrit (1 patient had a change in both). More patients who received infliximab had decreases in their total WBC (7.0%) compared with patients who received placebo (none). Significantly more patients who received infliximab had decreases in neutrophil count (17.5%) and experienced a lymphocytosis (13.2%) compared to placebo treated patients.

Review of the tabulated total WBC and neutrophils through week 30 show that the decreases in these laboratory values occurred sporadically for one or two measurements although patient 17019 may have had a sustained decrease in his total WBC and patients 21024 and 18004 appear to have a persistent neutrophilia. None of these were clinically significant. Review of the tabulated lymphocyte counts through 30 weeks reveals 7 infliximab-treated patients who appeared to have a persistent decrease in the lymphocytes, again not clinically significant (patients 17010, 23002, 13010, 12006, 28004, 20002, and 20006).

Table 3.30 Number of patients with changes in platelets and WBC counts through week 54.

	Placebo	3 mg/kg q 8 weeks	3 mg/kg q 4 weeks	10 mg/kg q 8 weeks	10 mg/kg q 4 weeks	All Infliximab	Treatmt effect p-value
Pts evaluated	86	89	86	87	80	342	
Platelets							
increase	7 (8.2%)	4 (4.5%)	1 (1.2%)	2 (2.3%)	2 (2.5%)	9 (2.6%)	0.13
decrease	4 (4.7%)	2 (2.2%)	8 (9.3%)	9 (10.3%)	4 (5.0%)	23 (6.7%)	0.15
Total WBC							
increase	14 (16.5%)	13 (14.6%)	9 (10.5%)	6 (6.9%)	9 (11.3%)	37(10.8%)	0.33
decrease	0 (0.0%)	8 (9.0%)	3 (3.5%)	8 (9.2 %)	5 (6.3%)	24 (7.0%)	0.04
Neutrophils							
increase	22 (25.9%)	22 (24.7%)	9 (10.5%)	7 (8.0%)	8 (10.0%)	46 (13.5%)	<0.001
decrease	0 (0.0%)	12 (13.5%)	16 (18.6%)	16 (18.4%)	16 (20.0%)	60 (17.5%)	<0.001
Lymphocytes							
increase	2 (2.4%)	8 (9.0%)	14 (16.3%)	10 (11.5%)	13 (16.3%)	45 (13.2%)	0.02
decrease	29 (34.1%)	20 (22.5%)	17 (19.8%)	16 (18.4%)	19 (23.8%)	72 (21.1%)	0.12
Monocytes							
increase	7 (8.2%)	11 (12.4%)	14 (16.3%)	17 (19.5%)	24 (30.0%)	66 (19.3%)	0.003
decrease	49 (57.6%)	44 (49.4%)	40 (46.5%)	44 (50.6%)	33 (41.3%)	161 (47.1%)	0.31

The number of patients who experienced these changes increased for all treatment groups between weeks 30 and 54 without an apparent treatment-dependent response. Table 3.31 shows the number of patients treated with placebo compared to all infliximab-treated patients who experienced changes in these hematological values at week 30 and week 54. In addition, the sponsor analyzed changes in WBC by the dose of methotrexat and there was no apparent correlation between methotrexate change and change in WBC.

Table 3.31 Comparison of hematological changes at week 30 and 54 for placebo-treated and all infliximab-treated patients

	Week 30		Week 54	
	Placebo	All Infliximab	Placebo	All Infliximab
Patients evaluated	85	342	85	342
Platelets				
increase	6 (7.1%)	5 (1.5%)	7 (8.2%)	9 (2.6%)
decrease	3 (3.5%)	20 (5.8%)	4 (4.7%)	23 (6.7%)
Total WBC				
increase	13 (15.3%)	24 (7.0%)	14 (16.5%)	37 (10.8%)
decrease	0 (0.0%)	21 (6.1%)	0 (0.0%)	24 (7.0%)
Neutrophils				
increase	17 (20.0%)	30 (8.8%)	22 (25.9%)	46 (13.5%)
decrease	0 (0.0%)	41 (12.0%)	0 (0.0%)	60 (17.5%)
Lymphocytes				
increase	2 (2.4%)	33 (9.6%)	2 (2.4%)	45 (13.2%)
decrease	23 (27.1%)	57 (16.7%)	29 (34.1%)	72 (21.1%)
Monocytes				
increase	5 (5.9%)	49 (14.3%)	7 (8.2%)	66 (19.3%)
decrease	44 (51.8%)	120 (35.1%)	49 (57.6%)	161 (47.1%)

Clinical Chemistry.

The clinical chemistry parameters measured are sodium, potassium, calcium, urea, creatinine, bilirubin, AST, ALT, alkaline phosphatase, total protein, and albumin. No patients had significant changes in sodium levels, and few patients had increases in calcium levels. Similarly, there were no significant increases in total protein or albumin. More patients treated with infliximab had increases in potassium but the increases were transient and not clinically significant. More patients treated with placebo had increases in urea and changes in creatinine were similar between patients treated with placebo or infliximab.

Table 3.32 presents the laboratory values indicative of liver function, i.e., bilirubin, alkaline phosphatase, AST and ALT. The number of patients with increases in bilirubin and alkaline phosphatase were similar among the infliximab and placebo treatment groups. Slightly more patients treated with infliximab had mild (<2 times the upper limit of normal) increases in AST/ALT at all timepoints.

Table 3.32 Number of patients with changes in bilirubin, alkaline phosphatase, AST and ALT through week 54.

	Placebo	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks	All Infliximab	Treatmt effect p-value
Pts evaluated	85	89	86	87	80	342	
Bilirubin							
increase	2 (2.4%)	1 (1.1%)	2 (2.3%)	5 (5.7%)	3 (3.8%)	11 (3.2%)	0.45
decrease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	NE
AST							
increase	20 (23.5%)	30 (33.7%)	35 (40.7%)	35 (40.2%)	27 (33.8%)	127 (37.1%)	0.12
decrease	4 (4.7%)	1 (1.1%)	0 (0.0%)	1 (1.1%)	3 (3.8%)	5 (1.5%)	0.17
ALT							
increase	25 (29.4%)	32 (36.0%)	40 (46.5%)	33 (37.9%)	22 (27.5%)	127 (37.1%)	0.08
decrease	3 (3.5%)	6 (6.7%)	6 (7.0%)	8 (9.2%)	5 (6.3%)	25 (7.3%)	0.68
Alkaline phos							
increase	13 (15.3%)	9 (10.1%)	13 (15.1%)	5 (5.7%)	6 (7.5%)	33 (9.6%)	0.15
decrease	3 (3.5%)	6 (6.7%)	6 (7.0%)	8 (9.2%)	5 (6.3%)	25 (7.3%)	0.68

The numbers of patients with changes in hepatic enzymes were compared between treatment groups by the degree of their increase (<2 times the upper limit of normal, ≥ 2 but <3 times the upper limit of normal, or ≥ 3 times), and by timepoint. Table 3.33 shows the number of patients with elevations in AST and ALT through week 54. Overall, the number of patients who had an increase in these enzymes was slightly higher among patients treated with infliximab. Most of the increases were <2 times the upper limit of normal and there was no apparent dose effect. The proportion of patients with an increase in AST and ALT at week 30 were similar. In other words, with continued exposure to infliximab through week 54, the proportion of patients who experienced an increase in their liver enzymes did not increase.

Table 3.33 Number of patients with an increase in AST & ALT by treatment group through wk 54.

	Placebo	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks
Pts evaluated	85	89	86	87	80
AST					
increase <2	20 (23.5%)	27 (30.3%)	35 (40.7%)	35 (40.2%)	23 (28.8%)
increase ≥ 2 but <3	3 (3.5%)	5 (5.6%)	4 (4.7%)	3 (3.4%)	6 (7.5%)
increase ≥ 3	1 (1.2%)	1 (1.1%)	1 (1.2%)	1 (1.1%)	2 (2.5%)
ALT					
increase <2	20 (23.5%)	28 (31.5%)	31 (36.0%)	27 (31.0%)	23 (28.8%)
increase ≥ 2 but <3	4 (4.7%)	4 (4.5%)	6 (7.0%)	7 (8.0%)	6 (7.5%)
increase ≥ 3	3 (3.5%)	4 (4.5%)	6 (7.0%)	4 (4.6%)	1 (1.3%)

Review of the tabulated AST, ALT, alkaline phosphatase and bilirubin through week 30 identified five patients who had sustained ALT elevations. One patient each also experienced sustained elevation in alkaline phosphatase and AST. All five of these patients were treated with infliximab and are described below. (Note: the trial period for this review is through week 30 so the tabulated laboratory values for the period following week 30 have not been submitted). Patient 02002 discontinued from the clinical study at week 30 due to the abnormal hepatic functions.

- Patient 11001 (3 mg/kg q 8 wks)

- Patient 33009 (3 mg/kg q 8 wks)

- Patient 01009 (3 mg/kg q 4 wks)

- Patient 07018 (3 mg/kg q 4 wks)

- Patient 02002 (10 mg/kg q 8 wks)

Discontinuations due to abnormal laboratory test results.

Four patients discontinued study treatment due to abnormal laboratory test results.

- Patient 01009 (3 mg/kg q 4 wks) had study treatment discontinuation due to worsening hyperglycemia, detected approximately 3 weeks after the sixth (week 18) infusion.
- Patient 02002 (10 mg/kg q 8 weeks group) had study treatment discontinuation due to abnormal hepatic function; The principal investigator did not attribute these abnormal liver chemistries to the patient's MTX administration.
- Patient 01016 (placebo) had study treatment discontinuation due to worsening iron deficiency anemia, detected 4 weeks after the third (week 6) infusion.
- Patient 07004 (placebo) had study treatment discontinuation due to thrombocytopenia (decreased platelet count) at week 10; the decrease in platelet counts began at week 2 and continued after study agent discontinuation.

Increases in AST/ALT according to MTX dose.

The sponsor evaluated changes in the hepatic enzymes through week 54 by the MTX dose patients received at baseline. For bilirubin, no patients had changes >2 times the upper limit of normal, and there was no apparent effect of concomitant MTX administration with infliximab. For alkaline phosphatase, there were also no apparent effects of higher doses of MTX with infliximab. Tables 3.34 and 3.35 summarize the effects of concomitant infliximab and MTX upon AST and ALT. Because the number of patients in each subgroup are relatively small, particularly for AST/ALT increases ≥ 2 but <3, and increases ≥ 3, no conclusions can be made. Review of these data suggest that proportion of patients receiving ≤ 12.5 mg MTX per week who had an increase of <2 times the upper limit of normal AST/ALT were similar among all of the treatment groups. For patients receiving higher doses of MTX, the proportion of patients with <2 times upper limit normal increase in AST/ALT was slightly higher among the infliximab treatment groups compared to placebo. The number of patients in each MTX dosing category are small which makes detection of an effect between infliximab and MTX upon enzyme increases ≥ 2 times the upper limit of normal difficult. The greatest number of patients received between 12.5 and 20 mg MTX per week. In this subgroup there appears to be a greater proportion of patients who received infliximab and who experienced an increase in their AST/ALT ≥ 2 but <3.

Table 3.34 Number of patients with increase in AST by baseline MTX dose through week 54.

	Placebo	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks
Any MTX dose					
Pts evaluated	85	89	86	87	80
increase <2	20 (23.5%)	27 (30.3%)	35 (40.7%)	35 (40.2%)	23 (28.8%)
increase ≥ 2 but <3	3 (3.5%)	5 (5.6%)	4 (4.7%)	3 (3.4%)	6 (7.5%)
increase ≥ 3	1 (1.2%)	1 (1.1%)	1 (1.2%)	1 (1.1%)	2 (2.5%)
MTX ≤ 12.5mg/wk					
Pts evaluated	24	28	26	24	18
increase <2	10 (41.7%)	6 (21.4%)	7 (26.9%)	13 (54.2%)	4 (22.2%)
increase ≥ 2 but <3	0 (0.0%)	1 (3.6%)	1 (3.8%)	1 (4.2%)	2 (11.1%)
increase ≥ 3	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
MTX >12.5mg/wk but <20 mg/wk					
Pts evaluated	43	40	40	45	40
increase <2	7 (16.3%)	13 (32.5%)	15 (37.5%)	13 (28.9%)	13 (32.5%)
increase ≥ 2 but <3	1 (2.3%)	4 (10.0%)	2 (5.0%)	2 (4.4%)	3 (7.5%)
increase ≥ 3	0 (0.0%)	1 (2.5%)	0 (0.0%)	1 (2.2%)	0 (0.0%)
MTX >20 mg/wk					
Pts evaluated	18	21	20	18	22
increase <2	3 (16.7%)	8 (38.1%)	13 (65.0%)	9 (50.0%)	6 (27.3%)
increase ≥ 2 but <3	2 (11.1%)	0 (0.0%)	1 (5.0%)	0 (0.0%)	1 (4.5%)
increase ≥ 3	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)	1 (4.5%)

Table 3.35 Number of patients with increase in ALT by baseline MTX dose through week 54.

	Placebo	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks
Any MTX dose					
Pts evaluated	85	89	86	87	80
increase <2	20 (23.5%)	28 (31.5%)	31 (36.0%)	27 (31.0%)	23 (28.8%)
increase ≥ 2 but <3	4 (4.7%)	4 (4.5%)	6 (7.0%)	7 (8.0%)	6 (7.5%)
increase ≥ 3	3 (3.5%)	4 (4.5%)	6 (7.0%)	4 (4.6%)	1 (1.3%)
MTX ≤ 12.5mg/wk					
Pts evaluated	24	28	26	24	18
increase <2	11 (45.8%)	8 (28.6%)	8 (30.8%)	11 (45.8%)	5 (27.8%)
increase ≥ 2 but <3	1 (4.2%)	1 (3.6%)	1 (3.8%)	1 (4.2%)	1 (5.6%)
increase ≥ 3	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
MTX >12.5mg/wk but <20 mg/wk					
Pts evaluated	43	40	40	45	40
increase <2	7 (11.6%)	14 (35.0%)	12 (30.0%)	10 (22.2%)	13 (32.5%)
increase ≥ 2 but <3	0 (0.0%)	1 (2.5%)	4 (10.0%)	5 (11.1%)	3 (7.5%)
increase ≥ 3	2 (4.7%)	4 (10.0%)	3 (7.5%)	3 (6.7%)	0 (0.0%)
MTX >20 mg/wk					
Pts evaluated	18	21	20	18	22
increase <2	4 (22.2%)	6 (28.6%)	11 (55.0%)	6 (33.3%)	5 (22.7%)
increase ≥ 2 but <3	3 (16.7%)	2 (9.5%)	1 (5.0%)	1 (5.6%)	2 (9.1%)
increase ≥ 3	0 (0.0%)	0 (0.0%)	3 (15.0%)	1 (5.6%)	0 (0.0%)

3.3.3.8 Conclusion regarding safety data from T22

- The comparison of adverse events in patients treated with infliximab and placebo is limited by the relatively small number of patients in each of the dosing regimens. Comparison of all infliximab treated patients compared to placebo does not provide a fair assessment of risk because of the great discordance in the number of patient-years in those exposed to infliximab compared to placebo.

- Overall, patients treated with infliximab experienced more adverse event compared to patients treated with placebo. A greater proportion of patients treated with infliximab discontinued study drug due to adverse event compared to placebo.

- Patients treated with infliximab may have a slightly higher risk of infections, particularly, upper respiratory tract infections. Patients may also have difficulty responding to milder infections such that more serious infections occur, e.g., urinary tract infections progressing to pyelonephritis, the need to be hospitalized for cellulitis.

- A greater proportion of patients treated with infliximab experienced infusion reactions and there were more cardiopulmonary and dermatological types of reactions in patients treated with infliximab.

- The development of HACA and any associated risk cannot be determined from the data collected to date from T22.

- A greater proportion of patients treated with infliximab developed autoimmune antibodies and there was one case of a lupus type of reaction in a patient treated with infliximab in T22 (ATTRACT). The number of patients and incidence of autoimmune reactions are too small to extrapolate to the patient population with rheumatoid arthritis.

- Treatment with infliximab may potentiate some of the adverse effects of MTX. A slightly higher proportion of patients treated with infliximab and MTX experienced ulcerative stomatitis and had mild elevations in their liver function tests. Although there were no serious adverse events that could be attributed to the combined therapies, the patients who discontinued therapy due to abnormal liver enzymes were treated with infliximab and MTX. As stated earlier, the numbers are too small to make any conclusions.

Appendix 3.A. List of patients who discontinued from T22 (ATTRACT).

		Reason for Discontinuation				
		Adverse event	Loss of Efficacy		Other	
Patient/ Dose	Last Infusion		No Δmed	Δ med/surg		Treatment Response
Placebo						
01010	3				Noncompliant	
01016	3	Fe def anemia				Responder
02005	3			X		
03005	3	CHF			Withdrew	
03008	5			X	Withdrew	
05009	4		X			
05013	2			X		
06022	3				Too far distance	
07004	4	Dec platelets				
08001	2			X		
10006	4				Noncompliant	
12008	5			X	(Died later)	
14001	4			X	(Died later)	
14009	8		X			
15003	1			X		
15008	4		X			
17015	3		X		LTFU	
18001	3			X		
19002	6			X		
19009	7		X			
19012	5	Toe gangrene				
20012	6		X			
21007	4			X		
21011	3			X		
24006	5			X		
26005	3		X		Withdrew	
30001	8	CP failure			Pt died	
30009	3		X			
32004	2			X	Withdrew	
32006	2	Hyperglycemia				
33002	2			X	Withdrew	
33011	6	L hip fracture				
Total n=32	Median=4	Total = 7	Total =7	Total =15	Total =3	

Appendix 3.A (continued) – List of patients who discontinued from T22

		Reason for Discontinuation				
		Adverse event	Loss of Efficacy		Other	
Patient/ Dose	Last Infusion		No Δ med	Δ med/surg		Treatment Response
3 mg/kg q 8 Wks						
01008	5		X		Withdrew	
02009	3				Left USA	
06002	4		X		Withdrew	
06016	3	Pulmonary embolus			Pt died	
07025	5			X		
08005	3	L facial warmth				Responder
11001	6		X			
19006	7		X		Withdrew	
20011	5		X			
25010	2	SOB				
27009	8			X		
28002	6			X		
30002	7			X		
31004	8		X			
31006	6		X			
Total n=15	Median=5	Total = 3	Total = 7	Total = 4	Total = 1	
3 mg/kg q 4 wks						
01009	6	Hyperglycemia				
06017	5			X		
07003	8		X			
14006	3			X	Withdrew	
21003	3		X			
24007	2	Pyelonephritis				
25004	5	Hives (reason for discontinuation)	X			
25012	6		X			Responder
28001	2	Bacteremia			Pt died	
30011	4		X			
Total n=10	Median 4.5	Total =4	Total=4	Total=2		
10 mg/kg q 8						
05008	8			X		
08004	7	Hip fracture				
18005	2	Lupus				
18009	4		X			
20009	4	Suicide attempt				
26007	7		X			
31009	6		X			
32003	8			X		
Total n=8	Median 6.5	Total = 3	Total= 3	Total = 2		

Appendix 3.A (continued) – List of patients who discontinued from T22

		Reason for Discontinuation				
		Adverse event	Loss of Efficacy		Other	
Patient/ Dose	Last Infusion		No Δmed	Δmed/surg		Treatment Response
10 mg/kg q 4 wks						
04018	7		X			
05012	8	Renal failure				
06014	5		X			
07006	5	L5/S1 disc			Withdrew	
11008	3		X			
11011	3	Sepsis				
15016	5	Chapped fingers				
17012	7	Increase trigeminal neuralgia			Withdrew	Responder
19014		Palpitations (reason for discontinuation)	X			Responder
27003	6	Breast Ca				
29003	6		X			
33006	7		X			
Total n=12	Median 5.5	Total = 6	Total = 2	Total = 3	Total = 1	

Appendix 3.B. Comparison of the Individual Components of the ACR.

Analytical method. The following tables provide the median and the median percent change for each of the individual components of the ACR at the specified visits through week 30.

The individual ACR components were summarized over time by calculating the percent improvement from baseline by using a method in which the last observation before a patient missed 2 consecutive evaluations was carried forward. Percent improvement from baseline was defined as the percent change from baseline to each follow-up visit for each patient, where the changes were calculated so that an improvement from baseline was a positive value. According to the protocol, no statistical analyses were to be performed on data when more than 25% of any treatment group had missing data because they discontinued efficacy evaluations. Because more than 25% of the placebo group were unavailable for efficacy evaluations after week 18, statistical analyses were not performed for the median percent changes from baseline over time for the individual clinical response assessments from that point forward. Percent change from baseline in RF was analyzed at weeks 10 and 30 by using ANOVA on van der Waerden normal scores for a test of the overall treatment effect and contrast statements for subsequent pairwise comparisons.

The following series of table provides the median for the number of patients actually evaluated at the given visit while the median % change is calculated as described above, i.e., the last value for that ACR component is carried forward. Consequently, the number of patients at the later visits for the median percent change would be greater than the number listed in the table.

Table B.1 Median and median % change in number of swollen joints through week 30

	Placebo	3 mg/kg q 8 weeks	3 mg/kg q 4 weeks	10 mg/kg q 8 weeks	10 mg/kg q 4 weeks
Pts randomized	88	86	86	87	81
Baseline					
Pts evaluated	88	86	86	87	81
Median	19	19	20	20	23
Week 2					
Pts evaluated	87	85	85	87	81
Median	17	15	14	15	16
Median % change	-11.0	-27.3	-21.4	-26.8	-25.0
Week 6					
Pts evaluated	85	85	83	84	80
Median	15	11	11	12	13
Median % change	-13.5	-41.5	-42.8	-33.3	-41.7
Week 10					
Pts evaluated	73	81	81	86	79
Median	14	11	11	10	11
Median % change	-17.1	-41.2	-42.9	-44.4	-46.2
Week 14					
Pts evaluated	69	83	81	85	77
Median	12	12	9	12	9
Median % change	-22.2	-32.0	-47.4	-47.1	-57.9
Week 18					
Pts evaluated	65	77	81	80	74
Median	13	10	7	9	9
Median % change	-17.8	-41.9	-50.0	-50.0	-58.3
Week 22					
Pts evaluated	61	79	79	81	71
Median	12	9	7	9	7
Median % change	-18.5	-50.0	-55.0	-57.1	-61.1
Week 26					
Pts evaluated	61	76	78	80	72
Median	11	10	7	7	5
Median % change	-18.8	-52.0	-63.3	-61.6	-70.6
Week 30					
Pts evaluated	73	79	83	84	79
Median	12	8	8	8	6
Median % change	-19.6	-51.5	-50.0	-60.0	-64.3

Table B.2 Median and median % change in number of tender joints through week 30

	Placebo	3 mg/kg q 8 weeks	3 mg/kg q 4 weeks	10 mg/kg q 8 weeks	10 mg/kg q 4 weeks
Pts randomized	88	86	86	87	81
Baseline					
Pts evaluated	88	86	86	87	81
Median	24	32	31	30	35
Week 2					
Pts evaluated	87	85	85	87	81
Median	26	19	20	19	21
Median % change	-4.1	-25.0	-28.6	-30.4	-32.6
Week 6					
Pts evaluated	85	85	83	84	80
Median	19	20	16	14	17
Median % change	-18.8	-35.0	-44.7	-42.4	-39.1
Week 10					
Pts evaluated	73	81	81	86	79
Median	18	14	15	14	15
Median % change	-25.0	-44.9	-41.9	-50.0	-44.5
Week 14					
Pts evaluated	69	83	81	85	77
Median	14	16	14	14	13
Median % change	-30.8	-45.5	-46.0	-51.1	-58.1
Week 18					
Pts evaluated	65	77	81	80	74
Median	17	9	13	10	10
Median % change	-27.2	-58.3	-50.0	-61.5	-60.0
Week 22					
Pts evaluated	61	79	79	81	71
Median	16	10	13	11	11
Median % change	-21.2	-50.0	-51.3	-57.1	-58.5
Week 26					
Pts evaluated	61	79	79	81	71
Median	14	10	9	9	7
Median % change	-21.2	-58.3	-64.0	-70.7	-63.9
Week 30					
Pts evaluated	73	79	83	84	79
Median	14	10	10	13	9
Median % change	-26.3	-59.2	-64.9	-57.6	-65.2

Table B.3 Median and median % change in patient's assessment of pain through week 30

	Placebo	3 mg/kg q 8 weeks	3 mg/kg q 4 weeks	10 mg/kg q 8 weeks	10 mg/kg q 4 weeks
Pts randomized	88	86	86	87	81
Baseline					
Pts evaluated	88	86	86	87	81
Median	6.7	7.0	6.9	6.7	6.6
Week 2					
Pts evaluated	87	86	86	87	81
Median	6.2	4.1	3.6	3.8	4.2
Median % change	-3.1	-36.3	-30.1	-36.7	-30.0
Week 6					
Pts evaluated	85	84	84	86	81
Median	5.9	3.9	3.0	3.8	3.8
Median % change	-5.6	-39.7	-43.1	-40.0	-43.5
Week 10					
Pts evaluated	73	83	84	86	78
Median	4.8	3.5	3.4	3.3	3.4
Median % change	-6.5	-48.9	-41.8	-48.5	-50.7
Week 14					
Pts evaluated	70	83	82	85	79
Median	5.0	4.1	2.9	3.3	3.1
Median % change	-7.4	-29.9	-40.2	-46.8	-50.7
Week 18					
Pts evaluated	66	78	81	82	75
Median	5.1	3.3	2.7	2.5	2.7
Median % change	-4.2	-40.6	-44.2	-58.8	-49.3
Week 22					
Pts evaluated	61	79	80	83	72
Median	4.5	3.6	3.3	3.7	3.3
Median % change	-9.2	-36.0	-39.2	-48.5	-42.9
Week 26					
Pts evaluated	61	76	79	81	72
Median	4.3	3.0	3.4	2.9	3.2
Median % change	-12.7	-47.7	-37.7	-55.3	-46.9
Week 30					
Pts evaluated	75	79	84	86	79
Median	4.9	3.4	3.3	3.3	3.8
Median % change	-5.7	-32.5	-42.9	-50.0	-35.2

Table B.4 Median and median % change in patient's global assessment of disease activity through week 30

	Placebo	3 mg/kg q 8 weeks	3 mg/kg q 4 weeks	10 mg/kg q 8 weeks	10 mg/kg q 4 weeks
Pts randomized	88	86	86	87	81
Baseline					
Pts evaluated	88	86	86	87	81
Median	6.2	6.6	5.7	6.4	6.0
Week 2					
Pts evaluated	87	86	86	87	81
Median	5.6	4.0	4.0	4.0	3.8
Median % change	-8.1	-22.2	-32.0	-32.3	-27.1
Week 6					
Pts evaluated	85	84	84	86	81
Median	5.7	3.8	3.0	4.1	3.5
Median % change	-11.2	-34.8	-50.8	-48.4	-39.0
Week 10					
Pts evaluated	73	83	84	86	78
Median	4.9	3.3	3.1	3.7	3.4
Median % change	-13.5	-45.0	-40.8	-51.6	-53.2
Week 14					
Pts evaluated	70	83	82	85	79
Median	4.6	4.6	2.9	3.7	2.9
Median % change	-17.7	-44.4	-47.9	-50.3	-56.7
Week 18					
Pts evaluated	66	78	81	82	75
Median	5.1	3.0	2.8	3.0	2.6
Median % change	-18.3	-54.8	-58.2	-55.6	-62.3
Week 22					
Pts evaluated	61	79	80	83	72
Median	4.9	3.5	3.1	3.4	3.6
Median % change	-18.0	-49.7	-50.9	-52.2	-56.0
Week 26					
Pts evaluated	61	76	79	81	72
Median	4.4	3.2	2.8	2.8	2.9
Median % change	-18.3	-53.9	-60.5	-60.4	-61.3
Week 30					
Pts evaluated	75	79	84	86	79
Median	4.6	3.3	3.0	3.7	3.3
Median % change	-13.0	-52.8	-59.2	-57.8	-59.4

Table B.5 Median and median % change in evaluator's global assessment of disease activity through week 30

	Placebo	3 mg/kg q 8 weeks	3 mg/kg q 4 weeks	10 mg/kg q 8 weeks	10 mg/kg q 4 weeks
Pts randomized	88	86	86	87	81
Baseline					
Pts evaluated	88	86	86	87	81
Median	6.5	6.1	6.2	6.4	6.0
Week 2					
Pts evaluated	87	85	85	84	81
Median	5.7	3.8	3.5	3.9	4.3
Median % change	-8.1	-22.2	-32.0	-32.3	-27.1
Week 6					
Pts evaluated	85	84	82	86	80
Median	5.0	3.4	2.9	3.0	3.5
Median % change	-11.2	-34.8	-50.8	-48.4	-39.0
Week 10					
Pts evaluated	73	83	79	84	79
Median	5.0	2.8	3.0	2.6	2.9
Median % change	-13.5	-45.0	-40.8	-51.6	-53.2
Week 14					
Pts evaluated	70	83	83	84	79
Median	3.7	2.6	2.8	3.0	2.4
Median % change	-17.7	-44.4	-47.9	-50.3	-56.7
Week 18					
Pts evaluated	65	77	80	80	75
Median	4.3	2.4	2.2	2.4	1.9
Median % change	-18.3	-54.8	-58.2	-55.6	-62.3
Week 22					
Pts evaluated	59	78	79	81	73
Median	4.0	2.6	2.5	2.7	2.5
Median % change	-18.0	-49.7	-50.9	-52.2	-56.0
Week 26					
Pts evaluated	61	75	79	78	70
Median	3.5	2.5	2.0	2.1	2.3
Median % change	-18.3	-53.9	-60.5	-60.4	-61.3
Week 30					
Pts evaluated	73	79	82	85	79
Median	4.0	2.6	2.4	2.6	2.6
Median % change	-13.0	-52.8	-59.2	-57.8	-59.4

Table B.6 Median and median % change in health assessment questionnaire (HAQ) through week 30

	Placebo	3 mg/kg q 8 weeks	3 mg/kg q 4 weeks	10 mg/kg q 8 weeks	10 mg/kg q 4 weeks
Pts randomized	88	86	86	87	81
Baseline					
Pts evaluated	88	86	85	87	81
Median	1.8	1.8	1.8	1.8	1.6
Week 2					
Pts evaluated	87	86	86	87	81
Median	1.6	1.5	1.4	1.5	1.5
Median % change	0	-8.9	-10.0	-12.5	-10.0
Week 6					
Pts evaluated	85	85	84	86	80
Median	1.6	1.5	1.3	1.4	1.5
Median % change	-1.7	-14.3	-21.3	-21.1	-13.0
Week 10					
Pts evaluated	74	83	83	86	80
Median	1.4	1.4	1.4	1.3	1.5
Median % change	-4.8	-17.3	-19.8	-25.0	-16.7
Week 14					
Pts evaluated	70	83	83	85	79
Median	1.4	1.4	1.4	1.3	1.5
Median % change	-1.7	-13.3	-21.1	-16.7	-20.4
Week 18					
Pts evaluated	66	78	81	82	74
Median	1.5	1.3	1.1	1.1	1.4
Median % change	-3.4	-22.3	-27.3	-28.6	-21.6
Week 22					
Pts evaluated	61	79	80	83	72
Median	1.3	1.4	1.1	1.3	1.3
Median % change	-4.9	-14.3	-26.7	-25.0	-18.8
Week 26					
Pts evaluated	62	75	79	81	72
Median	1.3	1.4	1.1	1.3	1.4
Median % change	-4.0	-13.7	-28.2	-25.0	-24.4
Week 30					
Pts evaluated	75	81	84	86	79
Median	1.4	1.4	1.1	1.3	1.4
Median % change	-3.4	-13.0	-28.6	-26.7	-23.8

Table B.7 Median and median % change in C-reactive protein through week 30

	Placebo	3 mg/kg q 8 weeks	3 mg/kg q 4 weeks	10 mg/kg q 8 weeks	10 mg/kg q 4 weeks
Pts randomized	88	86	86	87	81
Baseline					
Pts evaluated	88	86	86	87	81
Median	3.0	3.1	2.0	2.5	2.4
Week 2					
Pts evaluated	87	86	86	87	80
Median	2.8	0.6	0.4	0.5	0.6
Median % change	0	-73.1	-72.4	-70.8	-69.5
Week 6					
Pts evaluated	83	85	84	86	81
Median	3.0	0.6	0.5	0.7	0.7
Median % change	0.6	-65.1	-62.4	-63.8	-64.3
Week 10					
Pts evaluated	73	82	84	84	80
Median	2.4	0.6	0.5	0.7	0.6
Median % change	-9.9	-72.1	-69.4	-66.2	-71.5
Week 14					
Pts evaluated	67	83	83	84	79
Median	2.0	0.7	0.6	0.6	0.6
Median % change	-11.1	-55.3	-65.2	-65.8	-73.9
Week 18					
Pts evaluated	64	78	81	81	73
Median	1.6	0.7	0.5	0.4	0.5
Median % change	-9.9	-66.5	-68.1	-71.8	-73.6
Week 22					
Pts evaluated	60	78	79	81	71
Median	1.8	0.9	0.6	0.5	0.5
Median % change	-4.7	-57.0	-60.0	-65.3	-71.6
Week 26					
Pts evaluated	61	75	78	80	69
Median	1.4	0.5	0.5	0.5	0.5
Median % change	-9.0	-73.1	-63.0	-72.1	-73.3
Week 30					
Pts evaluated	76	78	84	83	79
Median	1.7	0.8	0.5	0.6	0.6
Median % change	-8.6	-59.5	-60.8	-67.6	-76.1

Table B.8 Median and median % change in duration of morning stiffness through week 30

	Placebo	3 mg/kg q 8 weeks	3 mg/kg q 4 weeks	10 mg/kg q 8 weeks	10 mg/kg q 4 weeks
Pts randomized	88	86	86	87	81
Baseline					
Pts evaluated	88	86	86	87	81
Median	120	90	120	120	120
Week 2					
Pts evaluated	86	85	86	84	80
Median	90	45	30	60	60
Median % change	0	-44.4	-55.6	-50.0	-50.0
Week 6					
Pts evaluated	84	85	82	85	81
Median	90	30	30	45	30
Median % change	0	-59.8	-75.0	-66.7	-57.8
Week 10					
Pts evaluated	73	82	82	86	80
Median	60	25	25	30	30
Median % change	-33.3	-66.7	-75.0	-75.0	-75.0
Week 14					
Pts evaluated	70	82	82	83	79
Median	60	30	18	30	30
Median % change	-22.5	-66.7	-76.4	-75.4	-75.0
Week 18					
Pts evaluated	64	78	80	82	75
Median	60	23	15	30	30
Median % change	-25.0	-66.7	-78.5	-83.3	-75.0
Week 22					
Pts evaluated	60	78	78	83	73
Median	45	30	20	30	15
Median % change	-25.0	-55.6	-75.0	-75.4	-75.0
Week 26					
Pts evaluated	61	75	78	81	71
Median	45	30	15	15	15
Median % change	-25.0	-59.1	-75.0	-86.7	-75.0
Week 30					
Pts evaluated	74	79	83	86	79
Median	45	30	15	30	15
Median % change	-33.3	-75.0	-75.0	-83.3	-75.0

Table B.9 Median and median % change in patient's assessment of fatigue through week 30 (based upon VAS)

	Placebo	3 mg/kg q 8 weeks	3 mg/kg q 4 weeks	10 mg/kg q 8 weeks	10 mg/kg q 4 weeks
Pts randomized	88	86	86	87	81
Baseline					
Pts evaluated	88	86	86	87	81
Median	6.7	6.5	7.1	6.7	6.8
Week 2					
Pts evaluated	87	86	86	87	81
Median	5.8	4.2	4.3	4.4	5.0
Median % change	-3.9	-29.6	-29.6	-24.6	-22.7
Week 6					
Pts evaluated	85	84	84	86	81
Median	6.2	4.5	3.4	5.0	4.9
Median % change	-2.4	-27.1	-32.9	-22.9	-25.7
Week 10					
Pts evaluated	73	83	84	86	78
Median	5.4	3.7	4.1	1.8	4.9
Median % change	-6.9	-29.5	-24.6	-27.5	-23.5
Week 14					
Pts evaluated	70	83	82	85	79
Median	5.0	3.7	4.1	4.8	4.9
Median % change	-11.6	-28.2	-28.3	-28.9	-32.0
Week 18					
Pts evaluated	66	78	81	82	75
Median	4.9	3.9	3.0	3.6	3.9
Median % change	-2.1	-31.2	-25.1	-40.2	-33.6
Week 22					
Pts evaluated	61	79	80	83	72
Median	4.9	3.5	3.6	4.2	3.8
Median % change	-6.1	-36.5	-31.5	-26.2	-36.0
Week 26					
Pts evaluated	61	76	79	81	72
Median	4.6	3.5	3.9	3.5	3.2
Median % change	-11.2	-19.2	-28.6	-35.2	-48.4
Week 30					
Pts evaluated	75	79	84	86	79
Median	5.7	3.8	4.4	4.1	3.9
Median % change	-7.7	-30.6	-22.4	-32.8	-33.7

Table B.10 Median and median % change in erythrocyte sedimentation rate at baseline and at week 30.

	Placebo	3 mg/kg q 8 weeks	3 mg/kg q 4 weeks	10 mg/kg q 8 weeks	10 mg/kg q 4 weeks
Pts randomized	88	86	86	87	81
Baseline					
Pts evaluated	87	86	86	87	80
Mean ± SD	49 ± 25	49 ± 23	52 ± 24	50 ± 24	49 ± 23
Median	39	40	45	44	42
Week 30					
Pts evaluated	70	75	80	78	75
Mean ± SD	42 ± 22	31 ± 23	33 ± 29	33 ± 25	32 ± 23
Median	35	24	21	26	30

Table B.11 Median and median % change in rheumatoid factor through week 30.

	Placebo	3 mg/kg q 8 weeks	3 mg/kg q 4 weeks	10 mg/kg q 8 weeks	10 mg/kg q 4 weeks
Pts randomized	88	86	86	87	81
% change at week 10					
Pts evaluated	72	82	84	83	79
mean ± SD	9.4 ± 66.4	-17.1 ± 32.3	-9.8 ± 39.7	-2.7 ± 131	91.2 ± 868.8
Median	0	-21.6	-14.5	-17.9	-12.2
% change at week 30					
Pts evaluated	75	77	84	82	79
mean ± SD	16.0 ± 85.2	-29.4 ± 37.6	-25.2 ± 41.9	-20.4 ± 168.1	46.1 ± 673.5
Median	0	-36.8	-31.9	-46.5	-31.1

Appendix 3.C. List of Patients who Experienced Serious Infections at Timepoints in T22 (ATTRACT)

Dose Group	Through Week 30	Weeks 30-54	After Week 54
Placebo	07008- UTI	15008 – gastroenteritis	12003 – pyelonephritis
	12008 – pneumonia; sepsis		
	19012 – gangrene; osteomyelitis		
	27005 – pyelonephritis; sepsis		
3 mg/kg q 8 wks			
	01008 – bronchitis; influenza	18003 – skin ulcer; herpes zoster	07011 – cellulitis; septic thrombophlebitis
3 mg/kg q 4 wks			
	11006 – pneumonia	32005 – cellulitis	04014 – cellulitis
	18002 – Strep pneumonia; TB		07009 – skin ulcer
	21003 – pancreatitis		22008 – orthopedic infection
	24007 – pyelonephritis		
	28001 – bacteremia; septic arthritis; osteomyelitis		
10 mg/kg q 8 wks			
	14002 – Strep pneumonia	02006 – ruptured appendix	09001 – viremia
	15009 – cellulitis	22001 – coccidioidomycosis	
	28004 – herpes zoster		
	30003 – influenza		
	31005 – pneumonia		
10 mg/kg q 4 wks			
	05012 – pyelonephritis; cellulitis	09008- pneumonia	04005 – ortho infection
	11011 – sepsis	12007 – Upper respiratory infection	05018 – ortho infection
	15016 – cellulitis (erysipelas)		

4.0 Review of the Safety and Efficacy Data from the Clinical Trial, C0168T14 (T14)

4.1 Background

This section reviews the safety and efficacy results from T14, the supportive (phase 2) clinical trial for the use of infliximab in patients with rheumatoid arthritis who are receiving methotrexate (MTX). Patients were enrolled into this study from 27 September 1994 until 5 July 1995. The last follow-up visit (week 26) was on 9 January 1996. The study was conducted at six European sites.

4.2 Study Design

Objectives. To determine the safety, tolerance and immunogenicity of multiple doses of infliximab alone or in combination with MTX and to compare the efficacy of multiple doses of infliximab alone, MTX alone, or infliximab in combination with MTX in patients with rheumatoid arthritis.

Dose and dose regimens. Patients with active RA who were being treated with MTX for a minimum of 6 months before study entry were enrolled into the trial. All patients who met inclusion/exclusion criteria were to be randomized to 1 of the following treatment groups, with 15 patients in each group:

Group I	MTX plus placebo infusion
Group II	MTX plus 1 mg/kg cA2 infusion
Group III	Placebo tablets plus 1 mg/kg cA2 infusion
Group IV	MTX plus 3 mg/kg cA2 infusion
Group V	Placebo tablets plus 3 mg/kg cA2 infusion
Group VI	MTX plus 10 mg/kg cA2 infusion
Group VII	Placebo tablets plus 10 mg/kg cA2 infusion

MTX was given at a dose of 7.5 mg/week for at least 4 weeks before randomization. Patients were randomized to 1 of the 7 treatment groups just before the first infusion on day 0. The MTX treatment was to be continued at a dose of 7.5 mg/week for an additional 26 weeks for patients in groups I, II, IV and VI. Infliximab infusions were administered at doses of 1, 3 or 10 mg/kg at day 0 and weeks 2, 6, 10 and 14 (five infusions) for patients in Groups II through VII. Clinical and laboratory assessments were performed at screening; day 0 (before the infusion); and through week 26.

Eligibility Criteria. The study population comprised men and women between the ages of 19 to 74 years. Patients in the study were to have a diagnosis of rheumatoid arthritis according to the revised 1988 criteria of the American Rheumatism Association. Treatment with MTX for at least 6 months before screening, with no breaks in treatment of more than 4 weeks during this period, was required. In addition, during the 4 weeks before screening, MTX must have been administered at a stable dose of 7.5 mg/week. Patients receiving corticosteroids were to be on a stable dose of 7.5 mg/day or less for at least 4 weeks before screening and had to agree to remain on this stable dose during participation in the study. All patients were to have active disease defined as the presence of 6 or more swollen joints and at least 1 of the following:

- Duration of morning stiffness of at least 45 minutes
- Six or more tender/painful joints
- Erythrocyte sedimentation rate (ESR) of at least 28mm/hr or C-reactive protein (CRP) of $\geq$ 15 mg/L

Duration of Treatment. All but 1 patient (in the placebo infusion plus MTX group) received at least 2 infusions of study medication. Ninety-one percent (91%) of all patients received at least 3 infusions, 79.2% received at least 4 infusions and 77.2% received all 5 infusions of study medication.

Criteria for Evaluation. Serum cA2 concentration (Pharmacokinetics) Serum concentrations of cA2 were determined by a monoclonal-based enzyme immunoassay (EIA) method. This assay was capable of detecting a serum cA2 concentration of at least 0.10 µg/ml.

Efficacy Assessment. The primary measure of efficacy was the total time of response based on Paulus 20% improvement during the 26-week evaluation period. Secondary measures of efficacy included the proportion of patients responding based on Paulus 20% and 50% improvement; the proportion of patients responding based on American College of Rheumatology (ACR) 20% and 50% improvement.

Safety Assessment. The safety of cA2 treatment was examined by evaluation of adverse events and by evaluating serial measurements of laboratory parameters and vital signs for the occurrence of abnormal trends. Serial serum samples were collected for the detection of human antichimeric antibody (HACA).

4.3 Study Results

4.3.1 Study Population.

A total of 101 patients (74 women and 27 men) from 6 centers were enrolled. The distribution of patients by treatment group is summarized in Table 4.1.

Table 4.1 Distribution of patients by treatment group

	Placebo	1 mg/kg Infliximab		3 mg/kg Infliximab		10 mg/kg Infliximab	
	MTX+	MTX+	MTX-	MTX+	MTX-	MTX+	MTX-
Pts treated	14	14	15	15	14	14	15

All but one patient (placebo infusion plus MTX) received at least 2 of the 5 infusions of study drug. Ninety-one percent of all patients received at least 3 infusions, 79.2% received at least 4 infusions and 77.2% received all 5 infusions. The proportion of patients who received all 5 infusions was higher among patients who received 3 mg/kg or 10 mg/kg doses of infliximab with or without MTX (80-100%) or among patients who received 1 mg/kg infliximab plus MTX (92.9%) and was lowest among patients in the placebo infusion plus MTX cohort (42.9%) and in the 1 mg/kg without MTX cohort (53.3%).

4.3.2 Discontinuations

Table 4.2 summarizes the number of patients who discontinued treatment and the reasons for discontinuation. The proportion of patients who discontinued treatment was highest among patients in the placebo infusion plus MTX group (57.1%) and in the 1 mg/kg infliximab without MTX cohort (46.7%). The most common reasons for discontinuation in these groups were lack of efficacy.

Table 4.2 Number of Patients who discontinued treatment in T14

	Placebo	1 mg/kg Infliximab		3 mg/kg Infliximab		10 mg/kg Infliximab	
	MTX+	MTX+	MTX-	MTX+	MTX-	MTX+	MTX-
Pts treated	14	14	15	15	14	14	15
Pts discontinued	8 (57.1%)	2 (14.3%)	7 (46.7%)	0 (0.0%)	2 (14.3%)	2 (14.3%)	3 (20.0%)
Reasons							
Adverse event	0	2	2	0	1	1	1
Lack of efficacy	8	0	5	0	1	1	2

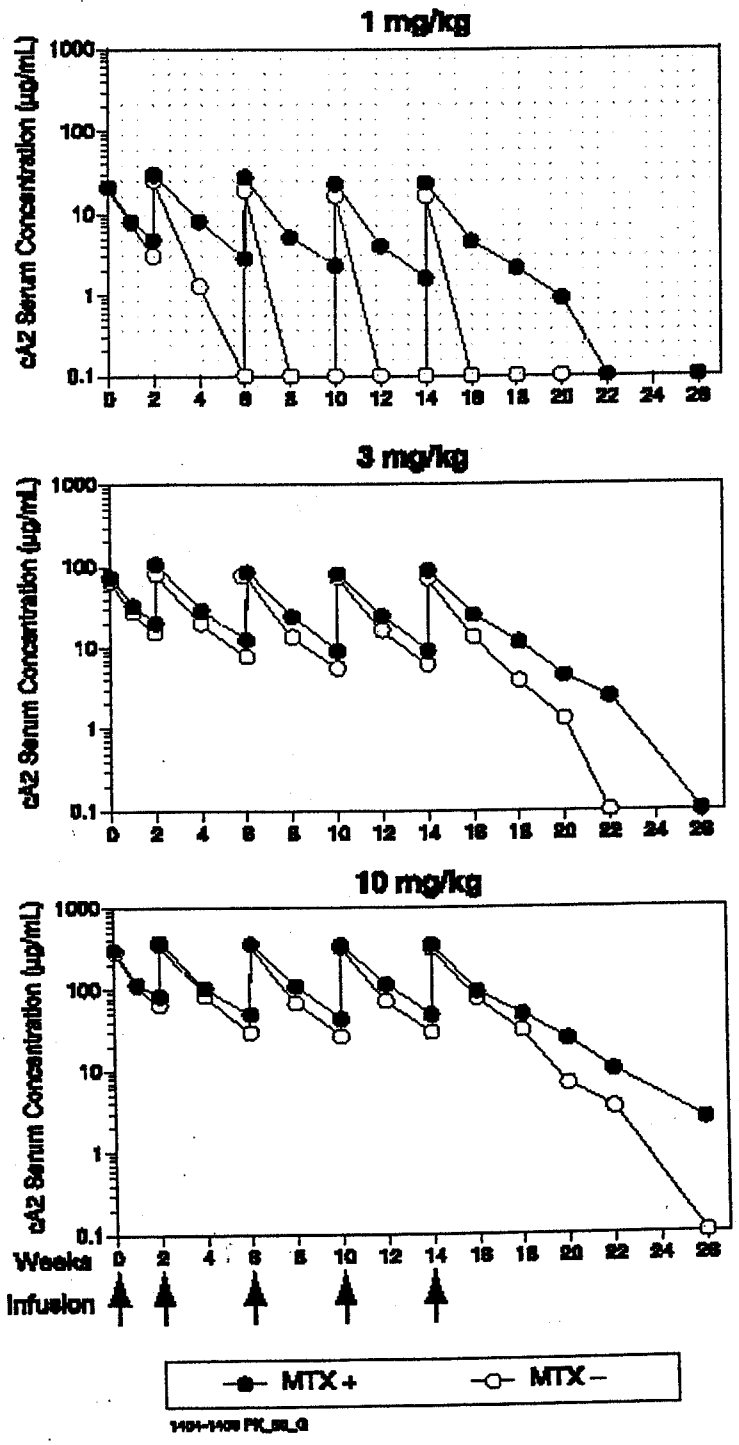
4.3.3 Infliximab Concentrations.

Blood samples for measurement of infliximab concentrations were obtained before and at 1 hour after each infusion (weeks 2, 6, 10 and 14) and at weeks 1, 4, 8, 12, 16, 18, 20, 22, and 26.

Figure 4.1 shows the median serum concentration of infliximab in the 6 dose groups that received infliximab. The median serum concentration of infliximab over time was dose-dependent and also demonstrated a significant effect of MTX in the 1 mg/kg treatment. Patients receiving 1 mg/kg infliximab without MTX showed a reduction in serum concentration of infliximab starting with the second dose of infliximab whereas stable levels were maintained in patients receiving 1 mg/kg infliximab plus MTX. At 3

or 10 mg/kg infliximab, serum concentration patterns were stable in patients receiving infliximab alone or in combination with MTX; serum concentrations of infliximab were consistently higher in patients receiving MTX.

Figure 4.1 Median serum infliximab concentration in the 6 dose groups receiving infliximab.



4.3.4 Clinical Response

The total duration of response based upon Paulus 20% improvement for the infliximab-treatment group except the 1 mg/kg without MTX group was significantly longer compared to placebo plus MTX group. The median duration of response ranged from 10.4 weeks to greater than 18 weeks in each of the infliximab treatment groups except for the 1 mg/kg without MTX group, with a median duration of response of 2.6 weeks compared to 0 weeks in the placebo plus MTX group.

The proportion of patients who had a 20% Paulus response at any time during the study was significantly greater in all infliximab treatment groups compared to placebo. With the exception of the 1 mg/kg infliximab without MTX group, response was sustained through 14 weeks (the last administered dose of infliximab). Clinical benefit was observed through 26 weeks (the last follow-up visit) in patients who received 3 or 10 mg/kg infliximab plus MTX. Figure 4.2 compares the percentages of patients achieving the Paulus 20% and ACR 20% criteria. Figure 4.3 compares the percentages of patients achieving the Paulus 50% and ACR 50% criteria

Figure 4.2 Percentage of patients who achieved the Paulus 20% and ACR 20% criteria

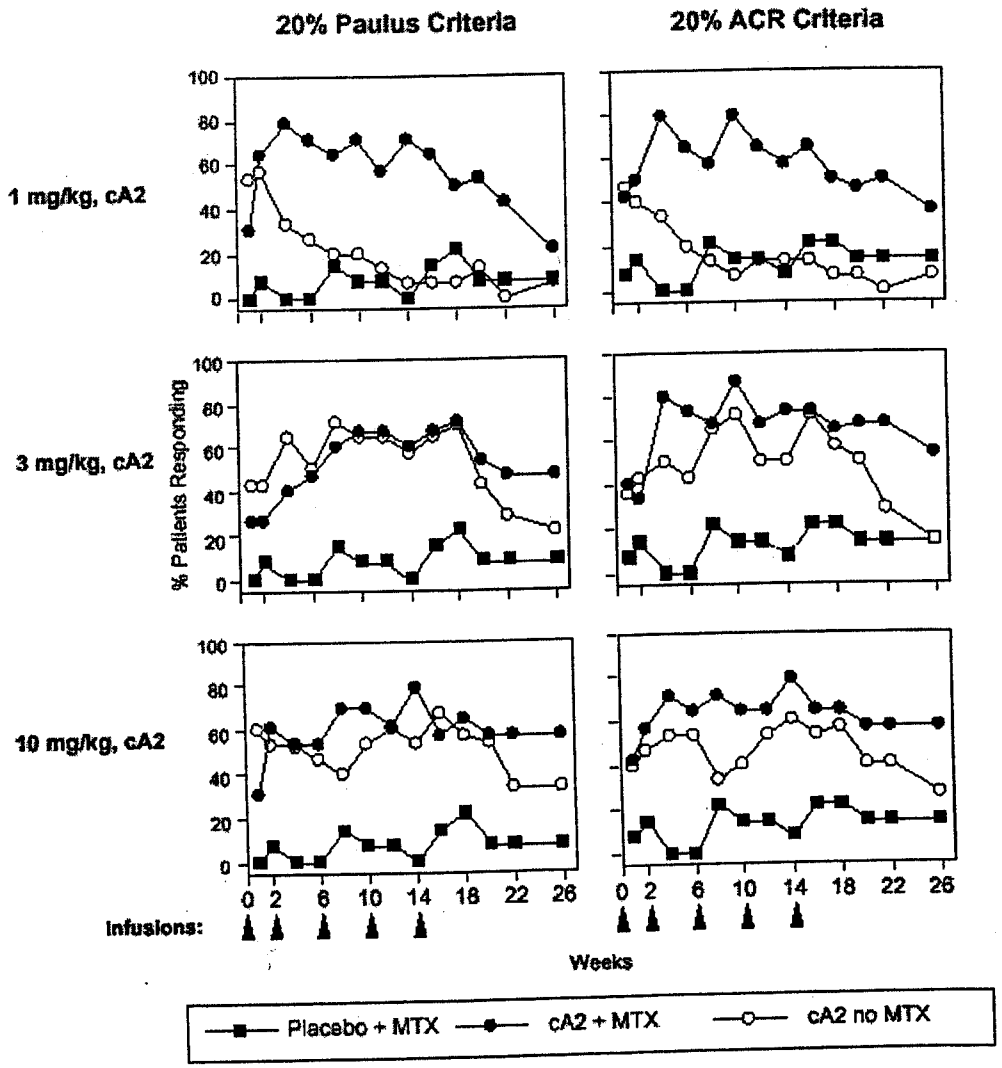
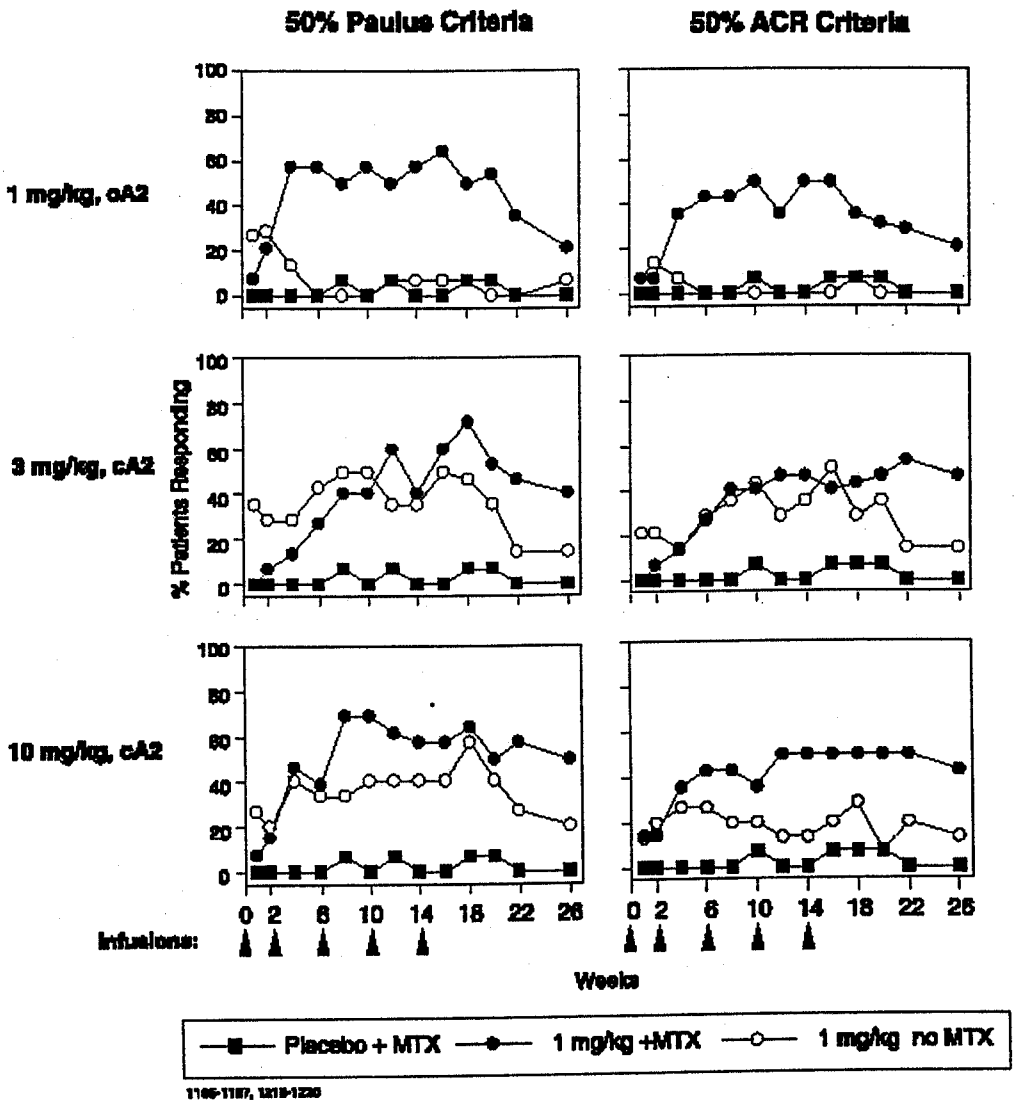


Figure 4.3 Percentage of patients who achieved the Paulus 50% and ACR 50% criteria.



4.4 Safety Results

All 101 patients enrolled in the trial were evaluated for safety. Only the serious adverse events, adverse events resulting in discontinuations, infections, infusion reactions, development of HACA and auto-antibodies, and changes in liver function tests will be presented in this report.

4.4.1 Deaths/Serious adverse events

No deaths were reported during the trial. One death, secondary to staphylococcal pneumonia with sepsis, occurred in a patient 15 weeks after her last treatment of 10 mg/kg infliximab.

Two patients had serious adverse events after their last infusion of infliximab.

- Patient 01006 developed bacterial endophthalmitis with *Citrobacter freundii* following elective cataract surgery performed 9 weeks after the final infusion of cA2. Despite intensive systemic and intravitreal antibiotic therapy, enucleation of the eye was required. The endophthalmitis was considered by the investigator to be possibly related to study drug.

- Patient 01009 developed tachycardia, night sweats, dry cough, shortness of breath and pleuritic chest pain approximately 3 weeks after the last infusion. Pericarditis was diagnosed by electrocardiogram (ECG) and a chest x-ray showed consolidation of the left lung base. An autoantibody screen revealed a positive ANA with a homogenous pattern and an elevated anti-double-stranded (ds) DNA. The patient was diagnosed as having drug-induced lupus and was treated with steroids as well as antibiotics for a possible superimposed pneumonia. She was discharged after 13 days in the hospital, with subsequent gradual resolution of symptoms and normalization of her antibody profile. Depression was also reported as a serious adverse experience with an onset 5 weeks after the lupus symptoms began. The symptoms were considered serious and probably related to study drug, except for depression, which was assessed as probably not related.

4.4.2 Discontinuations from the study

Seven patients, all who received cA2, discontinued treatment (i.e., did not complete all 5 scheduled infusions) because of adverse experiences. Of these, 5 patients withdrew because of infusion reactions, none of which were considered serious:

- Patient 02003 (1 mg/kg cA2 alone) developed dyspnea, erythema, headache and urticaria during infusion 3; the patient received no further infusions
- Patient 02014 (1 mg/kg cA2 plus MTX) developed chest pain, chills and paresthesias during infusion 5, which was not completed
- Patient 03006 (1 mg/kg cA2 plus MTX) developed urticaria the evening following infusion 3; infusions 4 and 5 were not administered
- Patient 01018 (3 mg/kg cA2 alone) developed urticaria during infusion 3 and during and following infusion 4; the patient did not receive infusion 5
- Patient 06001 (10 mg/kg cA2 alone) developed hypotension during each of the first 3 infusions; infusions 4 and 5 were not administered.

Of the remaining 2 patients who discontinued treatment due to adverse experiences:

- Patient 03014 (1 mg/kg cA2 alone) requested to be withdrawn because of an ongoing urinary tract infection and vaginitis occurring nearly 4 weeks following infusion 2 (vaginitis was considered by the investigator as probably not related to study drug)
- Patient 04023 (10 mg/kg cA2 plus MTX) requested to be withdrawn because of a rash which occurred 1 week after the fourth infusion (considered possibly related to study drug).

Two additional patients were discontinued from the trial, after completion of all 5 planned infusions, due to an adverse experience:

- Patient 01009 (3 mg/kg cA2 plus MTX) withdrew due to serious adverse experiences (symptoms related to lupus).
- Patient 02007 (10 mg/kg cA2 alone) withdrew due to increases in liver enzymes (considered as probably not related to study drug).

4.4.3 Infusion reactions

Twenty-three (23) cA2 patients (26.4%) and 3 placebo plus MTX patients (21.4%) had adverse experiences either during an infusion or within 2 hours after the end of an infusion. None of these events was serious; only 1 (hypotension in Patient 06001) was severe. Of the 26 patients, 19 experienced nonspecific reactions (e.g., headache, vomiting, etc.). These reactions tended to occur with the later infusions (infusions 3, 4 and/or 5); however, gastrointestinal reactions such as dyspepsia and diarrhea tended to occur with earlier infusions. The remaining 7 patients experienced erythema/urticaria (Patients 01018, 02003 and 03006), cardiovascular symptoms such as hypotension and chills (Patients 02014, 04007 and 06001) or both (Patient 06002). In all cases, symptoms resolved spontaneously or with appropriate treatment.

4.4.4 Infections treated with oral or parenteral antibiotic treatment

Overall, 23 patients developed ≥ 1 infections that required treatment with oral or parenteral antibiotics (Table 4.3). Two of these patients were treated with placebo and MTX. Of the 21 patients treated with infliximab, 13 also received MTX. The most common types of infection were upper respiratory tract infection (n=8) and urinary tract infections (n=9). One infection was serious (patient had endophthalmitis). The remaining infections resolved with appropriate antibiotic therapy.

Table 4.3 List of patients & types of infections requiring antibiotic treatment by exposure to MTX

Placebo	1 mg/kg infliximab	3 mg/kg infliximab	10 mg/kg infliximab
MTX+	MTX+	MTX+	MTX+
01019 – pharyngitis	01014 – pharyngitis	01006 – endophthalmitis, URI	none
01028 – pharyngitis, UTI*	01002 – pharyngitis, URI*, rhinitis, UTI*	01009 – pharyngitis, rhinitis	
	04020 – skin infection	01017 – pharyngitis	
	06003 – UTI*	01030 – UTI*	
		02004 – UTI*	
		04011 – toe infection	
		04017 – foot cellulitis	
		04022 – skin infection	
		06004 – UTI*	
MTX-	MTX-	MTX-	MTX-
none	06002 – UTI*	01013 – foot infection, moniliasis	01005 – herpes zoster
		01018 – UTI*	02010 – herpes zoster
		04018 – dental abscess	03004 – laryngitis
		06005- infected skin ulceration	

*UTI – urinary tract infection; URI – upper respiratory tract infection

After completion of participation into study T14, one patient experienced staphylococcal pneumonia with septicemia and is detailed below.

- Patient 01012 was a 64-year-old female patient with an 11-year history of progressive rheumatoid arthritis who was randomized to receive 10 mg/kg cA2 plus MTX. This patient had discontinued from the study due to lack of efficacy after the third of five planned cA2 infusions. Prior to her discontinuation from the study, the patient experienced mild headache following infusion 1, mild dyspepsia following infusion 2, and abnormal hepatic function following infusion 3. All of these adverse experiences were considered to be possibly related to study agent. The investigator noted that liver enzyme levels had normalized after discontinuation of a concomitant medication (diclofenac). Fifteen weeks after her last treatment with 10 mg/kg cA2, the patient died due to Staphylococcal pneumonia with septicemia. The investigator assessed this death as possibly related to study drug.

4.4.5 Antibody formation

4.4.5.1 Antinuclear antibodies (ANA) and anti-dsDNA

Patients were to have testing for ANA performed prior to the first infusion and at weeks 8, 16, and 26. If positive for ANA, the samples were tested first for anti-dsDNA antibody using the Farr assay and by the immunofluorescence techniques (IFT) on *Crithidia luciliae*. For a sample to be considered positive for anti-dsDNA antibody, the results from both assays had to be positive.

At baseline, 9 placebo-treated patients and 64 infliximab-treated patients were negative for ANA; 3 placebo-treated and 22 infliximab-treated patients were positive. Of the 9 placebo and 64 infliximab-treated patients with negative baseline values, 1 (11.1%) placebo and 28 (43.8%) infliximab-treated patients had positive findings at a later evaluation, with none of the placebo and 25 (39.1%) of the infliximab-treated patients having positive findings at the last evaluation. Of the 3 placebo and 22 infliximab-treated patients who were positive for ANA at baseline, none of the placebo and 4 (18.2%) infliximab-treated patients converted to negative findings at the last evaluation.

No apparent dose response was detected in the proportion of patients converting from negative to positive. It is noteworthy that the percentage of 1 mg/kg infliximab plus MTX cohort who converted from negative to positive (8.3%) was similar to results obtained in placebo patients (11.1%) while these percentages in all other infliximab-treated cohorts (with and without MTX) ranged from 33% to 60%.

Samples positive for ANA were tested for anti-dsDNA antibody. Seven infliximab-treated patients (8.1%) developed anti-dsDNA antibodies during the trial; none of the placebo patients developed anti-dsDNA antibodies. At the last evaluation 5 patients remained positive for anti-dsDNA antibodies. Based on late follow-up data, all patients had normalization of anti-dsDNA levels, with the exception of one patient who received 3 mg/kg infliximab (patient 04018), who had a positive finding based on Crithidia IFT, but not by Farr.

Only one patient, patient 01009, developed symptoms of signs of a lupus-like syndrome. Details of this patient are provided above under serious adverse events.

4.4.5.2 Human Antichimeric Antibodies (HACA)

Patients were to have blood samples collected for the measurement of HACA before the first infusion and at weeks 2, 6, 10, 14, 18 and 26. Patients could be evaluated for HACA if they had a baseline sample and at least 1 posttreatment sample in which infliximab could not be detected.

Table 4.4 summarizes the results for HACA responses. Of the 87 patients treated with infliximab, 60 could be evaluated for HACA. Of the 27 patients who could not be evaluated for HACA, 1 (3.7%) did not have posttreatment samples obtained and 26 (96/3%) had measurable infliximab concentrations in all of the posttreatment samples collected. Of the 60 patients treated with infliximab would could be evaluated for HACA, 15 (25%) had a positive HACA response. Higher proportions of patients who received infliximab alone had positive HACA responses than did those receiving infliximab in combination with MTX.

Table 4.4 Summary of HACA response in patients with detectable HACA

	1 mg/kg infliximab		3 mg/kg infliximab		10 mg/kg infliximab	
	MTX+ (n=14)	MTX- (n=15)	MTX+ (n=15)	MTX- (n=14)	MTX+ (n=14)	MTX- (n=15)
Pts evaluated	13	14	9	12	2	10
Positive HACA						
1:10	0	0	1	0	0	0
1:20	0	0	0	1	0	1
1:40	0	2	0	0	0	0
1:80	1	2	0	1	0	0
1:160	1	3	0	1	0	0
1:2560	0	1	0	0	0	0

The HACA data among patients who stopped returning for the follow-up visits (drop-outs due to lack of efficacy) was performed. The infliximab dose group having the largest proportion of patients dropping out due to lack of efficacy was the 1 mg/kg infliximab without MTX group (9 of 15 or 60.0% of patients). Of these 9 patients dropping out due to lack of efficacy, 7 had positive HACA findings prior to drop out and 2 had negative findings. Findings for the other infliximab dose groups (summarized below) do not indicate a relationship between lack of efficacy and HACA positivity.

- 1 mg/kg infliximab with MTX: 3/14 patients dropped out due to lack of efficacy (1 HACA-negative, 1 HACA-positive and 1 not evaluable due to interference of infliximab)
- 3 mg/kg infliximab with MTX: 1/15 patients dropped out due to lack of efficacy (HACA-positive)
- 3 mg/kg infliximab without MTX: 4/14 patients dropped out due to lack of efficacy (3 HACA-negative, 1 HACA-positive)
- 10 mg/kg infliximab with MTX: 2/14 patients dropped out due to lack of efficacy (both not evaluable)
- 10 mg/kg infliximab without MTX: 5/15 patients dropped out due to lack of efficacy (2 HACA-negative, 1 HACA-positive, 2 not evaluable).

These findings are consistent with the pharmacokinetic and efficacy findings in the 1 mg/kg infliximab without MTX group in that HACA development in these patients most likely contributed to decreased infliximab levels and the lack of efficacy observed in this group.

4.4.6 Clinical Chemistry – Liver function

The most common changes in clinical chemistry laboratory values observed among patients treated with infliximab were ALT (35.6%), AST (20.7%), and BUN/urea (25.8% and 19.6%, respectively). Changes in other laboratory parameters were relatively infrequent. The incidence of increases in BUN and urea were similar in both the infliximab and placebo cohorts. Increases in ALT and AST were observed only in infliximab-treated patients and are summarized in Table 4.5.

Thirty-one patients treated with infliximab had increases in ALT (11 in the 1 mg/kg, 10 in the 3 mg/kg, and 10 in the 10 mg/kg infliximab cohorts). Seventeen of these patients also had increases in AST (6 in the 1 mg/kg, 5 in the 3 mg/kg and 6 in the 10 mg/kg cohorts). An additional patients without an increase in ALT had an increase in AST (3 mg/kg infliximab plus MTX). There were 5 patients who had a persistent elevation in their AST and 10 patients who had a persistent elevation in their ALT through week 16 (2 weeks following the last infusion of infliximab) or week 26 (12 weeks following the last infusion of infliximab).

Table 4.5 Number of patients with changes in ALT and AST

	Placebo	1 mg/kg infliximab		3 mg/kg infliximab		10 mg/kg infliximab	
	MTX+ (n=14)	MTX+ (n=14)	MTX- (n=15)	MTX+ (n=15)	MTX- (n=14)	MTX+ (n=14)	MTX- (n=15)
AST							
increase	0 (0.0%)	4 (28.6%)	2 (13.3%)	4 (26.7%)	2 (14.3%)	2 (14.3%)	4 (26.7%)
decrease	1 (7.1%)	0 (0.0%)	1 (6.7%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ALT							
increase	0 (0.0%)	7 (50.0%)	4 (26.7%)	6 (40.0%)	4 (28.6%)	6 (42.9%)	4 (26.7%)
decrease	1 (7.1%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	2 (13.3%)

The median percent change from baseline to peak value in ALT and AST was calculated for each of the 7 treatment groups, as well as for all infliximab-treated, all infliximab without MTX-treated and all infliximab plus MTX-treated patients. Larger median increase in AST and ALT were observed in infliximab-treated patients (50% and 72%, respectively) than in placebo-treated patients (16% and 36%, respectively). When median percent changes from baseline to peak value were compared between patients who received infliximab plus MTX and those who received infliximab alone, larger median increases accompanied the concurrent use of MTX with infliximab (AST: 57% infliximab with MTX, 48% infliximab alone; ALT: 113% with MTX, 43% infliximab alone).

As noted above, one patient withdrew from the study due to increase in ALT and AST after receiving all 5 infusion of infliximab (patient 02007, 10 mg/kg plus placebo).

4.5 Conclusions

- The efficacy results from T14 support the clinical data generated in the pivotal trial T22.

- Results from T14 suggest that there is an interaction between the activities of MTX and infliximab. Patients who received 1 mg/kg of infliximab lost without MTX failed to maintain adequate serum concentrations of infliximab; in conjunction with the loss of serum levels of infliximab, the patients lost their clinical response. This interaction between MTX and infliximab was not as apparent at the two higher doses of infliximab. A potential interaction between the higher levels of infliximab and MTX is slightly more apparent with the Paulus criteria and at the higher ACR (ACR50, ACR70) compared to the ACR20.

- An interaction between MTX and infliximab may help explain the higher proportion of patients treated with both compounds who experience slight increases in their liver enzymes and experience ulcerative stomatitis compared to patients who are treated with MTX alone in both T14 and T22.

- It should be remembered that the formulation of infliximab used in T14 differs from that used in T22. In T14 the —— ormulation was used and the lots were similar to those used in the clinical trials evaluating patients with Crohn's disease. In contrast, the lyophilized formulation was used in T22. The sponsor reported to the agency the occurrence of a delayed hypersensitivity reaction in patients who received infliximab during the clinical investigation of infliximab as therapy for Crohn's disease. Eleven of the 12 documented cases occurred in patients who received the —— ormulation. The specific cause of these reactions to the product remain undefined. However, there is an immunogeneic component. The loss of serum levels and decreased efficacy seen in patients who receive infliximab without MTX probably relates to antibody neutralization of infliximab. It is possible that with the later lyophilized product, this neutralization effect may be markedly diminished. However, for the time being, infliximab should only be given in conjunction with MTX.

5.0 Consolidated safety data review

5.1 Clinical Trials Composing the Safety Database

This section reviews the safety database generated during the evaluation of infliximab for rheumatoid arthritis, Crohn's disease, as well as [redacted] and [redacted] The sponsor is conducting a long term (3 year) follow-up for participants in these developmental trials and these safety data are included. In addition, this review includes reports to the IND of serious adverse events made during the review of this submission. The focus of the review is upon deaths, malignancies, serious infections, infusion reaction, and autoimmune syndromes. Table 5.1 summarizes the clinical trials conducted by the sponsor in the clinical investigation of infliximab with the exclusion of clinical trials evaluating infliximab as [redacted]

Table 5.1 Characterization of Clinical Trials included in the safety database [redacted]

Study Number	Study Design	Dose Regimen	Number of Patients
Rheumatoid Arthritis			
T07	Phase 1, open label	5 mg/kg X 4 10 mg/kg X2	5 15
	Extended Treatment	10 mg/kg X3 10 mg/kg as needed	6 2
T09	Phase 2	Placebo x 1 1 mg/kg x 1 10 mg/kg x1	24 25 24
	open-label extension	3 mg/kg x1 10 mg/k x1 20 mg/kg x1	33 16 17
T14	Phase 2	placebo x 5 MTX+ 1 mg/kg x 5 MTX+ 1 mg/kg x 5 MTX- 3 mg/kg x 5 MTX+ 3 mg/kg x 5 MTX- 10 mg/kg x 5 MTX+ 10 mg/kg x 5 MTX-	14 14 15 15 14 14 15
T15	Phase 2	Placebo x1 5 mg/kg x1 10 mg/kg x1 20 mg/kg x1	7 7 7 7
T17	Open-label extension of T15	10 mg/kg x3	23
T18	Phase 1	10 mg/kg x 1 (12 weeks f/u)	10
T22	Phase 3 (ATTRACT) ongoing	Placebo 3 mg/kg q 8wks 3 mg/kg g 4 wks 10 mg/kg q 8 wks 10 mg/kg q 4 wks	86 89 86 87 80

Table 5.1(cont'd) Characterization of Clinical Trials included in the safety database

Study Number	Study Design	Dose Regimen	Number of Patients
Crohn's Disease			
T08	Phase 1	10 mg/kg x1 20 mg/kg x1	8 2
T11	Phase 2	1 mg/kg x1 5 mg/kg x1 10 mg/kg x1 20 mg/kg x1	5 5 5 6
T16	Phase 2/3	placebo x1 5 mg/kg x1 10 mg/kg x1 20 mg/kg x1	25 27 28 28
	Open label extension	10 mg/kg x 1	48
	Retreatment extension	placebo x 4 q 8 wk 10 mg/kg x 4 q 8 wk	36 37
T20	Phase 3	placebo x 3 5 mg/kg x 3 10 mg/kg x 3	31 31 32
T12	Phase 2	placebo 5 mg/kg 10 mg/kg 20 mg/kg	3 3 3 2
T00	Open label in various diseases	1 to 3 doses of 10 or 20 mg/kg over 17 weeks	9

Table 5.2 lists the number of events (both placebo and infliximab) that occurred in the clinical trials included in the safety database. Data regarding deaths and malignancies after participants complete the clinical trials are collected in T80, and naturally do not include any patients from the ongoing T22 (ATTRACT) trial in rheumatoid arthritis.

Table 5.2 Number of Safety Events for Clinical Trials evaluating Infliximab

	Rheumatoid Arthritis Trials						Crohn's disease Trials				Other
Event	**T7**	**T9**	**T14**	**T15/17**	**T18**	**T22**	**T8**	**T11**	**T16**	**T20**	**T12/T00**
Patients enrolled	20	73	101	28	10	428	10	20	108	94	20
Deaths											
during trial	-	-	-	-	-	8	-	-	-	-	-
after trial	3	2	3	1	1	-	1	1	1	-	1
Malignancies											
during trial	-	1	-	-	-	4	-	-	1	-	-
after Trial	2	2	2	2	-	-	-	-	2	4	2
Serious infections	-	2	2	2	-	34	1	-	5	3	2
Infusion reactions											
serious	-	1	-	-	-	1	-	-	3[a]	-	-
w/discontinuation	1	1	4	1	-	2	-	-		-	-
Autoimmune	-	-	1	-	-	1	-	-	1	-	-

[a] All three patients in T16 with serious infusion reactions discontinued study drug.

5.2 Narratives for the safety events occurring in the consolidated safety database

5.2.1 Serious infections

Rheumatoid arthritis trial - T22 (ATTRACT)

- Patient T22-07008 (placebo) is a 61-year-old woman with a 20-year history of rheumatoid arthritis, who successfully complete the 54 week study period (received all 15 scheduled infusions). She developed erosive gastritis at week 26 and a serious adverse event of urinary tract infection with fever and chills which required hospitalization at week 38. The investigator considered these events probably not related to study drug.

- Patient T22-12003 (placebo) is a 56-year-old man with a 3 year history of rheumatoid arthritis. Approximately 1 week after the week 46 infusion, the patient was hospitalized for treatment of pyelonephritis.

- Patient T22-12008 (placebo) is a 75-year-old woman with a 3-year history of rheumatoid arthritis. She was diagnosed with presumptive pneumonia and congestive heart failure after being discontinued from study at week 14 due to lack of efficacy. No organism was apparently identified and the patient subsequently developed sepsis (also reported as a serious infection) and died of cardiorespiratory failure secondary to RA-lung and intestinal gangrene. The investigator considered the all of these events unrelated to study agent.

- Patient T22-15008 (placebo) is a 62 year old woman with a 13-year history of rheumatoid arthritis experienced coughing, followed by diarrhea, vomiting, left abdominal pain, and fever. She was hospitalized for rehydration. CT scan of the abdomen revealed asymptomatic diverticulosis and cholelithiasis, and an abdominal obstruction series showed no obstruction but several areas of focal ileus. Stool, urine, and blood cultures were negative. These events occurred approximately 2 months after she discontinued therapy because of lack of efficacy. She had received 4 infusions of study drug (week 10). The investigator considered the diarrhea, vomiting, left abdominal pain, and fever probably not related to study agent.

- Patient T22-19012 (placebo) is a 56-year-old man with a 21-year history of RA and insulin-dependent diabetes mellitus. He developed peripheral gangrene (toes), skin ulceration, and osteomyelitis at week 14. The investigator considered these events related to study agent and discontinued study treatment.

- Patient T22-27005 (placebo) is a 53-year old woman with a 10-year history of rheumatoid arthritis. She was hospitalized with *E. coli* urosepsis in the setting of cardiac failure during week 10. This adverse event was associated with urinary retention, pyelonephritis, acute tubular necrosis, and renal insufficiency. Approximately 6 weeks later, she developed deep vein thrombosis of the right leg that resolved with treatment. The investigator considered all of these events unrelated to study agent.

- Patient T22-33011 (placebo) is a 65-year-old woman with a 19-year history of rheumatoid arthritis. She sustained a hip fracture resulting in discontinuation of study treatment and subsequently developed a wound infection approximately 4 weeks after her 6th study infusion (week 18). The investigator considered the event reasonably related to study agent.

- Patient T22-01008 (3 mg/kg q 8 wks) is a 59-year old man with a 22-year history of rheumatoid arthritis. Approximately 8 weeks after the 5th infusion of study drug (week 14) the patient developed bronchitis that did no respond to oral antibiotics. He was admitted to hospital for treatment of probable influenza and/or secondary bacterial pneumonia with dehydration. The investigator considered the bronchitis unrelated to study drug.

- Patient T22-07011 (3 mg/kg q 8 wks) is a 45-year old woman with a 9-year history of rheumatoid arthritis. Approximately 37 weeks after the 6th infusion of study drug (week 18), the patient developed

4 ulcers on her left calf. Four days later she was hospitalized for treatment of the left lower extremity stasis ulcers, superimposed left lower extremity cellulitis, and left lower extremity septic thrombophlebitis. The investigator considered both the stasis ulcers and cellulitis unrelated to study agent.

- Patient T22-18003 (3 mg/kg q 8 wks) is a 72 year-old woman with a 16-year history of rheumatoid arthritis. The patient discontinued study drug at week 50 due to skin ulcerations on her toes after having received 6 infusions of infliximab. Infusions at weeks 34 (placebo) and 38 (infliximab) were not administered because the patient had been exposed to open tuberculosis. The infusion at week 46 (infliximab) was also not administered because of a skin ulceration on her right great toe. Approximately 16 weeks after the last infusion of infliximab, the patient reported an ulcer on her right great toes. The patient was for treatment of the ulcer which was infected with methicillin *S. aureus* (MRSA). Approximately 22 weeks after the last infusion of infliximab, the patient presented with herpes zoster (the patient had a history of herpes zoster). The investigator considered the skin ulcers as probably related to the study agent and the herpes zoster probably not related to the study agent.

- Patient T22-4014 (3 mg/kg q 4 wks) is a 49-year old woman with a 6-year history of rheumatoid arthritis. Approximately 4 weeks after receiving the last infusion (total of 15) of infliximab, the patient presented to study center during the 58-week study visit with a 5-day history of right forearm swelling and "tightness." One day later, the patient was admitted to the hospital for treatment of her cellulitis. Blood cultures were negative. The investigator considered this event possibly related to the study drug.

- Patient T22-07009 (3 mg/kg q 4 wks) is a 69-year old white woman with an 8-year history of rheumatoid arthritis. The patient completed the full 54-week course of infusions (total of 15 infusions of infliximab). She began the retreatment phase of the study after a 4 month interval of no study drug infusions. Approximately 3 weeks after the first infusion in the retreatment phase, the patient presented with an enlarging sore on the end of her stump (she had a history of a left leg surgical amputation). Examination revealed a large eschar with surrounding erythema and tenderness as well as granulation tissue in the ulcer with a small amount of exudate. The patient was hospitalized for surgical debridement. The investigator considered the eschar/ulcer probably not related to the study agent.

- Patient T22-11006 (3 mg/kg q 4 wks) is a 67-year old man with a 9-year history of rheumatoid arthritis. The week 2 infusion of infliximab was postponed because the patient was febrile. The following day the patient was diagnosed with otitis media and antimicrobial therapy was initiated. The patient was subsequently hospitalized with the diagnosis of pneumonia. The investigator considered the pneumonia probably not related to the study agent.

- Patient T22-18002 (3 mg/kg q 4 wks) was a 63-year old woman with a 10-year history of rheumatoid arthritis. Several hours after the 8th infusion of study drug (week 26), the patient experienced multiple serious adverse events which included vomiting, abdominal pain, and cough. The cough, but not the other symptoms, was considered related to the study agent. She was hospitalized for rehydration. On week 31 the patient withdrew from the study due to a flare of her rheumatoid arthritis. Examination at that time revealed cervical lymphadenopathy. She complained of night sweats over the prior two weeks and had lost weight over the past 3 months. The patient was hospitalized; lymph node biopsy did not reveal malignancy but the patient was diagnosed with streptococcal pneumonia. The patient was again hospitalized one month later with the diagnosis of disseminated tuberculosis. The patient required ventilatory support and developed cholestatic jaundice which was attributed to the anti-tuberculous medication. The patient subsequently experienced a cardiopulmonary arrest, a right tension pneumothorax, hypoxic brain injury, and died. Bronchial alveolar lavage and cerebrospinal fluid culture both yielded *M. tuberculosis*, resistant to INH, rifampin, pyrazinamide, and clarithromycin.

- Patient T22-21003 (3 mg/kg q 4 wks) is a 73-year old woman with a 2-year history of rheumatoid arthritis. Approximately 3 weeks after the third infusion of infliximab (week 6), the patient was hospitalized with acute pancreatitis and gastrointestinal ulcer. These serious adverse events were both considered as probably not related to study agent. The patient was subsequently rehospitalized for dehydration which the investigator considered as not related to study agent.

- Patient T22-22008 (3 mg/kg q 4 wks) is a 50-year old woman with a 13-year history of rheumatoid arthritis. Approximately 2 weeks after the ninth infusion of infliximab (week 30), the patient presented with an infected bunion, which was treated for approximately 3 weeks with an antimicrobial. Approximately 6 weeks later the patient was hospitalized for a surgical procedure (unknown) to her second through the fifth metatarsal phalangeal joints. The patient was discontinued from the study at that time due to the infected bunion. She received 11 infusions of infliximab prior to discontinuation. The investigator considered the event as probably not related to the study agent.

- Patient T22-24007 (3 mg/kg q 4 wks) is a 46-year old woman with a 5-year history of rheumatoid arthritis. At the week 2 evaluation, the patient reported symptoms of back pain, fatigue, and chills in the evening; the second infusion of infliximab was administered. Three days later the patient was hospitalized with pyelonephritis which was considered as probably related to study agent Subsequent scheduled study agent infusions were discontinued due to the pyelonephritis and probable risk of repeat pyelonephritis in this patient with "one-kidney" condition. The investigator considered the pyelonephritis as probably related to study drug.

- Patient T22-28001 (3 mg/kg q 4 wks) was a 61-year old man with a 9-year history of rheumatoid arthritis. The patient was hospitalized with *S. aureus* bacteremia and septic arthritis twenty-two days after the second infusion of infliximab. The patient was diagnosed with osteomyelitis of the thoracic spine approximately 2 weeks after hospitalization which did not respond to two months of antimicrobial therapy. The patient subsequently experienced respiratory insufficiency and congestive heart failure attributable to possible pulmonary embolism. The patient died due to cardiopulmonary failure. The patient receive no additional study drug; the investigator considered the osteomyelitis of the spine, septic arthritis, and bacteremia as possibly related to the study drug.

- Patient T22-32005 (3 mg/kg q 4 wks) is a 65-year old woman with a 28-year history of rheumatoid arthritis. Approximately 4 weeks after receiving the 13th infusion of infliximab, the patient presented with cellulitis in the right leg/groin area and altered pigmentation of the right distal leg and hospitalized for treatment of cellulitis. The patient missed the week 50 study visit because of the cellulitis and discontinued from the study because of the cellulitis.

- Patient T22-02006 (10 mg/kg q 8 wks) is a 45-year old man with a 13-year history of rheumatoid arthritis. Approximately 9 weeks after receiving the last infusion of infliximab (week 38), he was diagnosed with a ruptured appendicitis. His postoperative course was uncomplicated. The patient was discontinued from the trial because of noncompliance. The investigator considered the ruptured appendix as probably not related to the study agent.

- Patient T22-09001 (10 mg/kg q 8 wks) is a 53-year old woman with a 4 year history of rheumatoid arthritis. Approximately 20 weeks after receiving her week 54 infusion of infliximab, the patient was hospitalized with fever, bilateral occipital headache, nonfocal posterior neck pain, bilateral myalgias of the lower extremities, and low back pain. The patient was discharged the next day with a diagnosis of probably viremia and headache. Her symptoms resolved in two weeks. The investigator considered the viremia as probably not related to study agent.

- Patient T22-14002 (10 mg/kg q 8 wks) is a 40-year old woman with a 15-year history of rheumatoid arthritis. Six days after the 7th infusion of infliximab (week 38), the patient was hospitalized for streptococcal pneumonia. The study agent was not discontinued. The investigator considered the pneumonia as probably not related to study drug.

- Patient T22-15009 (10 mg/kg q 8 wks) is a 44-year old woman with a 3-year history of rheumatoid arthritis. Approximately 5 weeks after the 6th infusion (week 18) of study drug, the patient had a rheumatoid nodule removed from the right hand. Four days later the surgical area became painful and started to drain. The patient was admitted two days later with cellulitis and lymphagitic spread. The patient had removal of bursa sac on the middle finger and was treated with antimicrobial therapy. Her postoperative course was uncomplicated. The investigator considered these events as probably not related to study drug.

- Patient T22-22001 (10 mg/kg q 8 wks) was a 70-year old woman with a 19-year history of rheumatoid arthritis. Approximately 2 weeks following the 11th infusion of study agent, the patient was hospitalized with anemia, hypercalcemia, hypomagnesemia, and hypokalemia. During a cholecystectomy, miliary granulations of the peritoneum were noted and biopsy/culture diagnosed coccidioidomycosis. The patient expired during the hospitalization. The investigator considered these adverse events as probably not related to study agent.

- Patient T22-28004 (10 mg/kg q 8 wks) is a 52-year old woman with a 7-year history of rheumatoid arthritis. Approximately 3 weeks after the 5th infusion (week 22) of infliximab, the patient developed herpes zoster and was hospitalized for antiviral therapy. The investigator considered the herpes zoster as probably not related to study agent.

- Patient T22-30003 (10 mg/kg q 8 wks) is a 60-year old woman with a 9-year history of rheumatoid arthritis. Approximately 18 days after the second infusion (week 2) of infliximab, the patient was hospitalized with shortness of breath, nausea, sore throat, muscle aches, chills, sweats, and possibility of sepsis. She was treated with parenteral antimicrobials and there was no evidence of sepsis. Her flu-like symptoms resolved. The investigator considered shortness of breath as probably not related to study agent.

- Patient T22-31005 (10 mg/kg q 8 wks) is a 57-year old man with a 25-year history of rheumatoid arthritis. Three days after the 3rd infusion (week 6) of infliximab, the patient was hospitalized and diagnosed with pneumonia and leukopenia. These adverse events resolved with therapy and the investigator considered them as probably not related to study drug.

- Patient T22-04005 (10 mg/kg q 4 wks) is a 52-year old man with a 4-year history of rheumatoid arthritis. Approximately 27 weeks after the 15th infusion of infliximab (week 54), the patient was hospitalized and treated for a *S. aureus* infection of a screw site of the hand with surgery and antibiotics. The investigator considered this adverse event as possibly related to the study drug.

- Patient T22-05012 (10 mg/kg q 4 wks) was a 74-year old woman with 36-year history of rheumatoid arthritis. Approximately 3 weeks after the 6th infusion (week 18) of infliximab, the patient was hospitalized and diagnosed with pyelonephritis. The pyelonephritis was considered as possibly related to study agent. One month after the 8th infusion of infliximab (week 26), the patient was hospitalized for cellulitis, bilateral hydronephrosis, and anemia. With the exception of bilateral hydronephrosis, the investigator considered all of these events as possibly related to study drug. The patient discontinued from additional study drug administration due to multiple serious adverse events. Approximately one month later the patient was diagnosed with large cell lymphoma involving the marrow, pelvis, and left inguinal lymph node. The lymphoma was noted to improve with chemotherapy and was considered as life-threatening and possibly related to study drug. She died during week 52, due to presumed cardiac arrythmia.

- Patient T22-05018 (10 mg/kg q 4 wks) was a 73-year old woman with a 6-year history of rheumatoid arthritis. Approximately 2 weeks after the 11th infusion (week 38) of infliximab, the patient underwent an elective left total knee replacement without complications. Approximately 3 weeks after the next infusion of infliximab, the patient was hospitalized with a diagnosis of an infected left knee and delayed closure. The investigator considered both the knee replacement and infection as probably not related to the study drug.

- Patient T22-09008 (10 mg/kg q 4 wks) is a 56-year old man with a 30 year history of rheumatoid arthritis. Approximately 2 weeks after the 11th infusion (week 38) of infliximab, the patient was hospitalized with pneumonia. The investigator considered the pneumonia as probably not related to study agent.

- Patient T22-11011 (10 mg/kg q 4 wks) is a 54-year old man with a 13-year history of rheumatoid arthritis. Approximately 2 days after the 3rd infusion (week 6) of infliximab, the patient was hospitalized with the diagnosis of sepsis. He was admitted to the ICU and was treated successfully with fluids, antibiotics, and pressor agents. No pathogen or specific source was identified. The investigator considered the event as possibly related to study drug.

- Patient T22-12007 (10 mg/kg q 4 wks) is a 49-year old woman with an 8-year history of rheumatoid arthritis. Approximately 3 weeks after the 10th infusion (week 34) of infliximab, the patient was hospitalized for possible sepsis and diagnosed with an upper respiratory tract infection. Her symptoms resolved with hydration. The investigator considered the event as possibly related to study drug.

- Patient T22-15016 (10 mg/kg q 4 wks) is a 48-year old woman with a 14-year history of rheumatoid arthritis. Approximately 3 weeks following the 4th infusion (week 10) of infliximab, the patient awoke with a high fever and selling and redness all over her face and was hospitalized the next day after failing to respond to oral antibiotics. The investigator considered the cellulitis as probably not related to study drug.

Other rheumatoid arthritis trials

- Patient T09-03006 (infliximab) is a 61-year-old male who developed an exacerbation of purulent bronchitis after a single dose of 1 mg/kg infliximab. The investigator considered this event reasonably related to study agent. The patient later died from mixed epithelioid Hodgkin's lymphoma. (see deaths)

- Patient T09-04003 (infliximab) is a 62-year-old woman who developed chills, fever, and retrosternal pain 2 weeks following the single infusion of 1 mg/kg infliximab. She was diagnosed with probable pneumonia and responded to treatment although no organism was identified. She subsequently had a pleural biopsy which showed rheumatoid nodule formation. The investigator considered the event reasonably related to study agent.

- Patient T14-01006 (infliximab) is a 69-year-old man with a 1-year history of rheumatoid arthritis who underwent an uneventful elective cataract removal 9 weeks after the fifth infusion of 3 mg/kg infliximab. The day of surgery, he developed severe left eye pain and was admitted with endophthalmitis due to *Citrobacter freundii*. Four days after cataract removal, the eye was eviscerated following failure of medical therapy. The investigator considered the event reasonably related to study medication.

- Patient T14-01009 (Infliximab) is a 36-year old woman with a 6-year history of rheumatoid arthritis, who experienced dyspnea, pleuritic chest pain, and flaring of rheumatoid arthritis symptoms 6 days before the fifth scheduled infusion of 3 mg/kg infliximab. The patient had a questionable infiltrate, was treated with antibiotics, and her symptoms resolved. She then was re-hospitalized 3 weeks later with pleuritic chest pain, shortness of breath, dry cough and night sweats and was diagnosed as having possible drug-induced lupus but was treated for possible superimposed pneumonia with gradual resolution of symptoms. These investigator considered these events reasonably related to study agent.

- Patient T15/T17-02003 (placebo) is a 59-year-old woman with rheumatoid arthritis, who developed septic olecranon bursitis approximately 6 weeks after the placebo infusion. Wound cultures grew *Klebsiella pneumonia*. The investigator considered the bursitis possibly related to study medication.

- Patient T15/T17-03004 (infliximab 5 mg/kg + 10 mg/kg x 3) is a 31-year old man with a 1-year history of rheumatoid arthritis, who developed cellulitis of the arm at the injection site, 4 days following the second infusion. The investigator considered the event related to study agent.

Crohn's disease trials

- Patient T08-01007 (infliximab) is a 40-year old man with Crohn's disease. The patient had an endoscopic evaluation prior to enrollment. Seven days after a single infusion of 10 mg/kg of infliximab, the patient developed symptoms of an acute abdomen and 10 days after infusion a Hartmann procedure was performed (closure of the rectum to allow regression of the anoperineal disease). After surgery the patient developed sepsis and ARDS and was treated in the ICU. This resolved and the patient was discharged from the hospital approximately 3 weeks later. The investigator considered the perforation as not related to cA2.

- Patient T16-01007 is a 35-year-old woman with a 3-year history of Crohn's disease who received 1 infusion of 10 mg/kg cA2 in the initial treatment phase followed 5 weeks later by a 10 mg/kg open-label infusion. One month after the second infusion she was seen by her local physician with a 1- to 2-week history of shortness of breath, cough, pleuritic chest pain and fever and was hospitalized with worsening infiltrates and hypoxia. Four days after admission she demonstrated clinical and radiographic improvement on a regimen of intravenous steroids and parenteral antibiotics. The investigator assessed the adverse experience as possibly related to study agent.

- Patient T16-03002 was hospitalized with trilobar pneumonia, which resolved following treatment with erythromycin, gentamicin and bactrim.

- Patient T16-08002 was a 61-year-old man with a 30-year history of Crohn's disease. The patient began to experience malaise, fatigue, dry cough and low-grade fever approximately 7 months following the single infusion of 10 mg/kg open-label infliximab. Despite extensive diagnostic evaluation, no clear etiology of the signs and symptoms was established. An eventual diagnosis of B-cell lymphoma was made. The investigator reported these events as possibly related to the study agent.

- Patient T16-16001 was a 39-year-old woman with a 6-year history of Crohn's disease. Three weeks after initial infusion of 20 mg/kg infliximab, the patient developed acute diarrhea and fever after eating at a Chinese restaurant. The patient was hospitalized, and blood cultures were positive for *Salmonella* sp. The investigator regarded this event as probably not related to study agent.

- Patient T16-22001 was a 27-year-old woman with a 1 ½-year history of Crohn's disease. Twelve days after the third infusion of 20 mg/kg infliximab the patient was admitted to the hospital with a 3-day history of right upper abdominal pain. Ultrasound findings showed a doubled gall bladder wall without calculi and a CT scan revealed the presence of free fluid around the gall bladder. She was treated for acalculous cholecystitis. The investigator assessed this event possibly related to the study agent.

- Patient T20-02002 (infliximab) was a 29-year-old female patient with an 11-year history of Crohn's disease who received 2 infusions of 10 mg/kg cA2 given 2 weeks apart. Approximately 3 weeks after the last infusion, the patient was admitted to the hospital with shortness of breath, fever, and nausea and vomiting. The final diagnosis was pneumonia with an unusual presentation. The investigator assessed the pneumonia as possibly related to study agent. The patient was not given any further infusions of infliximab.

- Patient T20-16002 (infliximab) presented with furunculosis (abscess) of the right arm and of the right leg approximately 2 months after the third infusion of 10 mg/kg infliximab. The abscess on the right leg was drained and the culture showed a staphylococcal species. The investigator assessed this event as probably related to study agent.

- Patient T20-18006 (infliximab) is a 31-year-old female patient with a 7-year history of Crohn's disease who received 3 infusions of 10 mg/kg cA2. She had a history of anal abscess and 2 months after her last infusion she was hospitalized because of a spontaneously-draining anal abscess. The investigator considered the event as possibly related to study agent.

Other clinical trials

- Patient T12-02001 was a 31-year-old man with a 1-year history of [redacted] Six days following an infusion of infliximab, the patient developed an abdominal cellulitis due to Group A streptococci from an infected wound site. His gastrointestinal symptoms worsened and he had a [redacted] performed for fulminant [redacted], 13 days following the infusion of infliximab. The investigator assessed the events as not related to study drug.

- Patient T00-02002 was a 41-year-old woman with a 7-year history of [redacted] One day after infusion of 10 mg/kg cA2, the patient developed a fever and blood cultures were positive for coagulase negative staphylococcus. Two days after the infusion, the central venous catheter was removed. The investigator assessed this event as not related to study agent.

5.2.2 Deaths

Rheumatoid arthritis trial – T22 (ATTRACT)

A total of 8 patients have died during the 54 week study period of T22. Five patients died during the first 30 weeks and three died between 30 and 52 weeks. A summary for each of these patients follows.

- Patient T22-12008 (placebo) was a 75-year-old woman with a 3-year history of rheumatoid arthritis. Approximately 6 weeks after the 5th infusion of study drug (week 14), she developed cardiac failure and pneumonia and was hospitalized, but continued to deteriorate despite appropriate therapy and subsequently developed sepsis although cultures were negative. Following a presumptive diagnosis of RA-lung or MTX-lung, treatment with corticosteroids and continued cardiorespiratory support resulted in some improvement. Approximately 1 month later, however, her condition began to deteriorate again with worsening of cardiopulmonary congestion, bacterial growth of *Pseudomonas aeruginosa* in tracheal cultures, and ileus with segmental gangrene of the smaller intestine requiring emergency laparotomy. The patient died during surgery. The investigator considered all events as probably not related to study agent.

- Patient T22-14001 (placebo) was a 52-year-old woman with a 4-year history of rheumatoid arthritis. She received a total of 4 infusions of study agent which were discontinued because of lack of efficacy and, approximately 1 month after the last infusion, the patient was found dead at her home by relatives. The cause of death was attributed by autopsy to be interstitial lung disease, heart failure, and pericardial effusion. The investigator classified these events as probably not related to study agent.

- Patient T22-30001 (placebo) was a 59-year-old man with a 6-year history of rheumatoid arthritis. Eighteen days after the eighth infusion (at week 26), the patient developed an acute abdomen. Emergency surgery revealed ischemic small bowel, necrotic large bowel, and ischemic and necrotic liver, and the abdomen was closed as these conditions were irreparable and the prognosis was thought to be dismal. The patient died shortly thereafter of cardiopulmonary failure. The investigator considered these events as probably not related to the study agent.

- Patient T22-06016 (3 mg/kg q 8 wks) was a 58-year-old woman with a 2-year history of rheumatoid arthritis. Approximately 2 weeks after receiving the third infusion of study agent (week 6), the patient developed a deep vein thrombosis of the right arm and bilateral pulmonary emboli. An embolectomy was planned but no venous access could be obtained and the patient died. The investigator considered the pulmonary embolus as probably unrelated to study drug.

- Patient T22-28001 (3 mg/kg q 4 wks) was a 61-year-old man with a 9-year history of rheumatoid arthritis. After having received 2 infusions of study agent, he was hospitalized with *S. aureus* bacteremia and septic arthritis of the left knee. Subsequent scheduled study agent infusions were discontinued due to the bacteremia. Approximately 1 week after resolution of the septic arthritis, the patient developed osteomyelitis of the thoracic spine. Approximately 2 months later, respiratory insufficiency and congestive heart failure developed due to suspected pulmonary embolism or underlying pulmonary fibrosis. The patient did not respond to treatment and died. The investigator considered the bacteremia and osteomyelitis but not the worsening respiratory insufficiency and uncompensated heart disease as possibly related to study drug.

- Patient T22-18002 (3 mg/kg q 4 wks) was a 63-year-old woman with a 10-year history of rheumatoid arthritis who received 8 infusions of infliximab. Five months after randomization, she experienced joint inflammation, fever, and weight loss and became dehydrated, presumably secondary to vomiting. Two months later, she had cervical lymphadenopathy and complained of 2 weeks of night sweats. Lymph node biopsy showed tuberculosis with no malignancy. Subsequent susceptibility testing demonstrated that the organism showed multiple drug resistant. She experienced cholestatic jaundice and antitubercular treatment was discontinued. She aspirated and required cardiopulmonary resuscitation. Resuscitation was complicated by a pneumothorax, hypoxic brain damage and subsequent death. (See serious infections)

- Patient T22-22001 (10 mg/kg q 8 wks) was a 70-year-old woman with a 19-year history of rheumatoid arthritis. She had received 11 infusions of study agent (week 38) when she was hospitalized due to a weak, confused, anemic condition. In preparation for gall bladder surgery, she was diagnosed with coccidioidomycosis ("Valley Fever") and treated with amphotericin B but died on approximately 1 month later while still in the hospital. The investigator considered the event unrelated to study agent.

- Patient T22-05012 (10 mg/kg q 4 wks) was a 74-year old woman with a 36-year history of rheumatoid arthritis. She was diagnosed with lymphoma before week 30. This patient died from presumed cardiac arrhythmia during week 52. The last of eight infusions of study agent had been given at week 26. (see malignancies)

Deaths during other clinical trials

In other clinical trials evaluating infliximab, there were no deaths in patients with either rheumatoid arthritis or Crohn's disease trials. The sponsor has been collecting clinical follow-up on participants of the developmental trials for the three years following the patient's participation under C016T80. A narrative of deaths reported under this follow-up protocol follow and include 3 patients whose death occurred after the 3 year reporting period.

Deaths After Study Participation

Information collected as part of a long-term safety follow-up for patients who had participated in studies with infliximab (C0168T80) included data for 10 patients who died during the 3-year period following their participation in an infliximab study (3 additional patients died after the 3-year follow-up period); all had received infliximab. Brief narrative summaries of these events are provided below.

Patients with rheumatoid arthritis

- Patient T07-01004 was a 59-year-old man with a 13-year history of rheumatoid arthritis. He received 2 infusions of infliximab (10 mg/kg). His medical history was significant for mild left ventricular failure. He died in August 1995 (approximately 3.25 years post infusion) from coronary artery disease. This event occurred after the 3-year follow-up period.

- Patient T07-01014 was a 76-year-old man with a 14-year history of rheumatoid arthritis. He received 2 infusions of infliximab (10 mg/kg) in early 1993. Thirty-eight months post infusion the patient presented with anorexia and a 3-month history of epigastric pain brought on by eating. Endoscopy identified a gastric mass. Histopathology following a partial gastrectomy showed an ulcerated poorly differentiated mucinous adenocarcinoma with lymph node involvement. No further information is available on this patient except that he died in December 1996, 44 months post-infusion. This event occurred after the 3-year follow-up period.

- Patient T07-01020 was a 48-year-old man with a 16-year history of rheumatoid arthritis. He received 2 infusions of infliximab (10 mg/kg infusions separated by 2 weeks). Eighteen months after the final infliximab infusion, he developed enlarged axillary and neck lymph nodes. Results of a biopsy of a supraclavicular lymph node showed a high-grade B-cell non-Hodgkin's lymphoma (NHL). The patient died 10 months after diagnosis.

- Patient T09-03006 was a 60-year-old man with a 16-year history of rheumatoid arthritis who received 1 infusion of infliximab (1 mg/kg). Approximately 6.5 months after the study agent infusion a left axillary mass was noted. Results of biopsy revealed a mixed epithelioid Hodgkin's lymphoma. The patient received 1 course of chemotherapy, but subsequently developed respiratory failure and died 9 months after the infliximab infusion.

- Patient T09-04002 was a 54-year-old man with a 15-year history of rheumatoid arthritis who received an open-label 3 mg/kg infliximab infusion. He did not respond to this therapy and was discontinued from study 4 weeks after the open-label treatment. The patient had a history of antral gastritis, hypertension, empyema and a recurring right-sided pleural effusion. Approximately 5 months after the infusion, the patient was admitted to hospital for increased breathlessness, a cough and sputum production associated with an empyema *(Streptococcus intermedius*). His hospital course was complicated by a moderate left pneumothorax and a right subtotal pneumothorax. No further information is available on this patient except that he died approximately 20 months after the infliximab infusion, from pneumonitis.

- Patient T14-01012 was a 64-year-old woman with an 11-year history of rheumatoid arthritis who was randomized to receive MTX 7.5 mg/week plus 10 mg/kg infliximab. She discontinued treatment after her third infliximab infusion because of lack of efficacy. Approximately 14.5 weeks after the last infusion, she was hospitalized with hypotension and decreased consciousness and was found to have staphylococcal pneumonia. She was treated with vasopressors and antibiotics but she became septic, developed multi-organ-system failure and died 1 day after hospital admission.

- Patient T14-01021 was a 73-year-old man with a 4-year history of rheumatoid arthritis. He had a history of ischemic heart disease, peptic ulcer disease and tuberculosis. He received five 1 mg/kg infusions plus MTX. He died 15 months after the last infliximab infusion from complications of coronary artery bypass surgery.

- Patient T14-01024 was a 65-year-old man with an 18-year history of rheumatoid arthritis. His medical history was remarkable for prior myocardial infarction and gastrointestinal hemorrhage. He received five 1 mg/kg infliximab infusions plus MTX. He died of a myocardial infarction 1 year post infusion.

- Patient T17-03009 was a 43-year-old woman with a 4-year history of rheumatoid arthritis. She received 1 infusion of 20 mg/kg infliximab during C0168T15 and 1 infusion of 10 mg/kg on while participating in C0168T17. She withdrew from the study because of lack of efficacy following the second infusion. 16 months after her last infusion the patient presented with shortness of breath and developed supraventricular tachycardia with worsening shortness of breath and chest pain. She developed electromechanical dissociation arrest and was resuscitated. A large pericardial effusion was diagnosed and drained. She was transferred to a tertiary referral center, where her neurological exam showed her to be unresponsive to painful stimuli, with no corneal reflexes and no cough or gag

reflexes. A head CT was obtained that showed a subarachnoid hemorrhage. She was pronounced dead 16 months after her last infliximab infusion.

- Patient T18-01002 was a 73-year-old woman with a 6-year history of rheumatoid arthritis who received 1 infusion of 10 mg/kg of infliximab. Study personnel were informed that the patient died of a myocardial infarction 24 months after the study infusion. The myocardial infarction was accompanied by congestive heart failure, paroxysmal ventricular tachycardia, atrial fibrillation, and chronic renal failure.

Patients with Crohn's Disease

- Patient T08-01002 was a 26-year-old woman with a 12-year history of Crohn's disease. She received a single 10 mg/kg infusion of infliximab. Approximately 4 years after the infusion, she was admitted to hospital for food poisoning (pathogen unknown). Approximately 2 weeks later, she developed chest pain irradiating into the left arm, jaw, back and shoulders. She was hospitalized where an ECG revealed ST-elevation in V2-V6, I and AVL. She died in the hospital on the day of admission, approximately 4 years after her treatment with infliximab. Autopsy revealed the cause of death to be an infarction of the left ventricular wall. This event occurred after the 3-year follow-up period for T80.

- Patient T11-02001 was a 52-year-old man with a 29-year history of Crohn's disease. The patient received a single 1 mg/kg infusion of infliximab. Approximately 11 weeks after his infusion he was diagnosed with *Clostridium difficile*. Subsequently, he developed *Pneumocystis carinii* pneumonia and cytomegalovirus secondary to his immunosuppressive therapy (which included cyclosporine). He died approximately 5 months post-infusion, with cause of death listed as immunosuppression.

- Patient T16-08002 was a 61-year-old man with a 30-year history of Crohn's disease. The patient initially received placebo, followed by an open-label infusion of 10 mg/kg infliximab and retreatment with 3 placebo infusions. The patient developed fever, melena, anemia and thrombocytopenia after the third placebo infusion. A diagnosis of B-cell lymphoma was made 9 ½ months after the 10 mg/kg infliximab infusion. Approximately 8 months after the infliximab infusion, during his first cycle of chemotherapy, the patient developed cardiac failure secondary to sepsis and died.

5.2.3 Malignancies

Rheumatoid Arthritis – T22 (ATTRACT)

- Patient T22-05012 (10 mg/kg q 4 wks) was a 74-year-old female with a 36-year history of rheumatoid arthritis. Approximately 3 weeks after receiving the sixth infusion (at week 18), the patient was diagnosed with pyelonephritis which was treated with ciprofloxacin. She was treated the following month for continued pyelonephritis which was considered possibly related to study agent. The patient continued to receive all 8 scheduled infliximab infusions through week 26. One month after the last infusion, she developed a left lung infiltrate, anemia, renal failure, bilateral hydronephrosis and confusion, and was considered as possibly having lymphoblastic lymphoma. She underwent bilateral stent placements to relieve bilateral renal obstruction secondary to a diffuse retroperitoneal process. Following additional evaluation, she was diagnosed with B-cell and received chemotherapy with radiological improvement. The investigator considered this event as possibly related to study agent, and was ongoing as of week 30. The patient died approximately 1 year after study entry, of presumed cardiac arrhythmia.

- Patient T22-27003 (10 mg/kg q 4 wks) was a 59-year-old female with a 1-year history of rheumatoid arthritis treated with MTX, and prior breast cancer and mastectomy of the left breast. Nine days after having received the sixth infusion of study agent (week 18), the patient was diagnosed with recurrent adenocarcinoma of the breast with metastases to the spine. The investigator considered the adenocarcinoma as probably not related to study agent.

- Patient T22-27008 (10 mg/kg q 4 wks) was a 62-year-old male with a 12-year history of rheumatoid arthritis. After having received 4 infusions of study agent (through week 10), the patient was noted to have actinic keratoses on the face and was subsequently diagnosed with invasive, well-differentiated squamous cell carcinoma of facial skin, considered as possibly related to study agent. The cancer was considered resolved after excision of lesions on the patient's right cheek and temple. Approximately 4 months later, after the patient had received 8 scheduled study drug infusions (week 26), a skin lesion biopsy on the neck revealed malignant melanoma (Clark's level II) which was excised; the lesion healed with no complications. The investigator considered this event possibly related to study agent.

- Patient T22-25007 (10 mg/kg q 8 wks) was a 60-year old female with a 20-year history of rheumatoid arthritis. Three days after receiving the week 46 infusion (infliximab), she began experiencing rectal bleeding. Approximately 1 month after completion of all 15 scheduled infusions (week 54) she was diagnosed with rectal adenocarcinoma, moderately differentiated, with superficial ulceration and diverticulosis. The investigator judged the intermittent diarrhea, rectal bleeding, and positive hemoccult test to be probably not related to study agent.

- In addition, during the review of this submission, the sponsor reported to the IND an additional malignancy. The patient is a 58-year old woman enrolled into T22. The patient received study drug through week 70. Approximately 2 weeks later, a biopsy of a lymph node in the groin diagnosed squamous cell carcinoma. The patient identifier and study treatment is unknown.

Other Studies in RA

- Patient T09-03011 was a 56-year-old woman with rheumatoid arthritis who developed a pathologic clavicle fracture, 1 week after receiving a single dose of 10 mg/kg of infliximab. Subsequent mammography was non-diagnostic, whole body scintigraphy was compatible with multiple blastic lesion changes secondary to malignant disease and sonography revealed an 8-mm tumor of the breast. Excisional biopsy of an axillary node showed histologic findings of an anaplastic carcinoma, consistent with a ductal breast cancer primary. The investigator considered this event to be unrelated to study treatment.

Non-RA Studies

- Patient T16-08002 was a 61-year-old man with a 30-year history of Crohn's disease who received a single open-label infusion of 10 mg/kg of infliximab. Baseline lymphopenia was noted at the initial screening but a repeat lymphocyte count 2 weeks later was acceptable for enrollment. Eight months after his infliximab infusion, the patient developed a fever, malaise, anemia, and thrombocytopenia. An abdominal CT scan showed splenomegaly and splenic and renal infarcts. Endoscopy of the upper gastrointestinal tract revealed duodenal ulcers and a polyp; biopsy diagnosed B-cell lymphoma. Chemotherapy was started but the patient died 13 days later from cardiac failure secondary to Aspergillus sepsis.

Malignancies after participation in rheumatoid arthritis studies

- Patient T07-01020 was a 48-year-old man with a 16-year history of rheumatoid arthritis. He received 2 infusions of infliximab (10 mg infusions separated by 2 weeks) with concomitant prednisone. Eighteen months after the final infliximab infusion, he developed enlarged axillary and neck nodes. Biopsy results of a supraclavicular node showed a high-grade B-cell non-Hodgkin's lymphoma. The patient died 2 months after diagnosis.

- Patient T09-03006 was a 61-year-old man with a 16-year history of rheumatoid arthritis who received 1 infusion of infliximab at a dose of 1 mg/kg. Approximately 6.5 months after his only infliximab infusion, he developed an enlarged axillary lymph node that was biopsied and revealed Hodgkin's lymphoma (mixed cellularity type). His subsequent course was complicated by pneumonia and adult respiratory distress syndrome, and he died 9 months after his single infliximab infusion.

- Patient T14-04007 was a 59-year-old woman with a 7-year history of rheumatoid arthritis. She received 5 infusions of infliximab (3 mg/kg) over a 14-week period. Seventeen months after the last infliximab infusion, she presented with hypercalcemia and rib and clavicle fractures. Bone marrow biopsy results and laboratory data were diagnostic of myeloma. As of the last follow-up information available, the patient was doing well on a salvage regimen.

- Patient T15/T17-03004 was a 52-year-old man with RA , who developed a Clark's level II superficial spreading melanoma 4.5 months after receiving 2 infusions of infliximab (5 mg/kg and 10 mg/kg) in protocols C0168T15 and C0168T17. The melanoma developed in a pre-existing irregularly pigmented macule that had been present for several years, but had recently become pruritic and turned darker. A wide excision was performed with clear margins. No recurrence has been reported.

- Patient T15/T17-03005 was a 63-year-old woman with a 4-year history of rheumatoid arthritis who received 3 infusions of 10 mg/kg of infliximab. Approximately 27 months after the last infusion, the patient was found to have a small tumor that was determined to be a basal cell carcinoma of the skin of the lower left leg. The tumor was removed by laser surgery.

- Three additional malignancies were reported in rheumatoid arthritis patients after the 3-year cut-off (stomach cancer, colon carcinoma, and lymphoma, 44, 41 months and approximately 6 years after last infusion, respectively).

- A 65 year old woman with rheumatoid arthritis was diagnosed with colon carcinoma approximately 41 months after an infusion of 1 mg/kg followed by an infusion of 3 mg/kg of infliximab.

- Poorly differentiated mucinous adenocarcinoma with lymph node involvement in a 76 year old man with rheumatoid arthritis. He received 2 infusion of infliximab (10 mg/kg) approximately 3 ½ years prior to his death.

- Patient T07-01003 was a 62-year old male with a 5-year history of rheumatoid arthritis who had received 2 infusions of infliximab (10 mg/kg 2 weeks apart). Approximately 6 years after receiving the last dose of infliximab, periaortic and iliac lymphadenopathy was discovered on CT scan and the patient also underwent 2 punch biopsies of the left inguinal lymph nodes which revealed predominantly large cell follicular lymphoma. The patient was alive at the time of the report.

Malignancies after participation in studies other than rheumatoid arthritis

The following 7 post-study malignancies were reported during the long-term safety follow-up, for non-rheumatoid arthritis patients.

Infliximab-treated patients

- Patient T16-03006 was a 40-year-old woman with a 4-month history of Crohn's disease who received one infusion with 5 mg/kg infliximab. The patient had ongoing hyperthyroidism (Graves' disease) and a nodular thyroid that had been treated with tapazole for more than a year. Twenty-one months after the infliximab infusion, the nodule had increased in size and a needle aspirate was performed which revealed malignant cells. The patient underwent a total thyroidectomy with the finding of a papillary carcinoma that was completely excised with no extension into the capsule.

- Patient T16-06001 was a 64-year-old man with a 5-year history of Crohn's disease who received 5 infusions of 10 mg/kg of infliximab. Approximately 4 months after the last infusion, the patient was diagnosed with prostate cancer. The patient underwent a radical prostatectomy for carcinoma of the prostate. The tumor was confined to the prostate and considered to have been cured by the surgery.

- Patient T20-16007 was a 57-year-old woman with an 11-year history of Crohn's disease who received 3 infusions of 5 mg/kg of infliximab. During the year following the end of the trial, the patient was hospitalized twice for relapses of Crohn's disease. A colonoscopy was performed but the cecum could not be visualized. A barium enema revealed 75 cm of ileum affected by Crohn's disease and a stenosis. Despite further medical therapy and enteral nutrition, the stenosis remained. An ileocecal resection performed 16 months after the last infusion of study drug revealed a signet cell carcinoma (Dukes C1) with one positive lymph node.

- Patient T20-18017 was a 34-year-old woman with an 8-year history of Crohn's disease who received 3 infusions of 5 mg/kg of infliximab. This patient was found to have anal carcinoma 6 months after the last infusion. The carcinoma was detected during surgical removal of perianal tag. The patient received post-operative radiotherapy and as of July 1998, there was no evidence of recurrence.

- A single case of non-Hodgkin's lymphoma (NHL) was observed at the National Cancer Institute in an [redacted] patient with a baseline [redacted] who received infliximab on a [redacted] This patient died.

Placebo patients

- Patient T20-22001 (placebo) was a 34-year-old male with a 15-year history of Crohn's disease who received 3 infusions of placebo. Approximately 3 years after her last infusion a skin lesion on the left knee was diagnosed as spindle cell carcinoma and resected in its entirety.

- Patient T20-22013 (placebo) was a 46-year-old woman with a 14-year history of Crohn's disease who received 3 infusions of placebo. Approximately one year after the last infusion, a surgical fistulectomy was performed. The fistula recurred and a seton was placed. CT scan of the abdomen performed approximately 21 months after the last infusion and diagnosed renal cell carcinoma of the left kidney.

Additional reports to the IND

[redacted]

5.2.4 Serious Infusion Reactions

No serious infusion reactions in T22 were reported through week 54. However, during the review of this license application, the sponsor submitted a report of a serious infusion reaction to the IND. The patient is a 67-year old woman who developed dizziness, shortness of breath, followed by seizure activity shortly after infusion at week 86 had begun. The patient had had an 8 week interval without study drug, i.e., missed week 82 and last infusion was at week 78. The patient identifier and dosing group remains blinded at this time.

In all Studies, 4 infusion reactions (0.3% of all infliximab infusions) were graded as serious. Three of the 4 serious infusion reactions occurred in a Crohn's disease study, T16 (all resulting in discontinuation and 1 occurred in the rheumatoid arthritis study, T09 (not resulting in discontinuation). No serious infusion reactions were reported in the ATTRACT (T22) study through week 54. These four infusion reactions are described below.

- Patient T09-01004 was a 65-year-old woman with a 12-year history of rheumatoid arthritis, who had a relatively mild infusion reaction during the second scheduled infusion of 3 mg/kg consisting of fever and an erythematous rash that was treated with an antihistamine. Because of residual drowsiness, the patient remained in the hospital for a few more hours than required per protocol, resulting in the

event could not be regarded as serious on clinical grounds. This patient was HACA positive.

- Patient T16-07002 was a 34-year-old woman with a 3-year history of Crohn's disease, who received an initial 5 mg/kg infusion. Two minutes into a 10 mg/kg second infusion, developed shortness of breath, numbness of the left arm and lips, pain in the abdomen, hip, knee and back, flushing, nausea, and chills. She received intravenous antihistamines and corticosteroids and all symptoms resolved within 2 hours. No further infliximab was administered. Dyspnea was the symptom considered serious, and the patient was discontinued from the study. This patient was HACA positive.

- Patient T16-09001 was a 48-year-old woman with a 4-year history of Crohn's disease who received an initial 5 mg/kg infliximab infusion and, 10 minutes into a 10 mg/kg second infusion developed severe flushing, abdominal pain, palpitations, chest tightness, shortness of breath, urticaria and hypertension, all of which resolved without treatment within 4 to 7 minutes of stopping the infusion. No further infliximab was administered. Hypertension, chest pain, dyspnea and palpitations were considered serious. This patient was discontinued from the study and was HACA negative.

- Patient T16-21002 was a 35-year-old man with a 7-year of Crohn's disease who developed lightheadedness, chest tightness and bronchospasm 30 minutes into the second infusion of 10 mg/kg and experienced hypotension. The infusion was discontinued and symptoms began to resolve within 10 to 20 minutes of stopping the infusion; no treatment was given and no further infliximab was administered as this patient was discontinued from the study. His symptoms and hypotension persisted for approximately 20 minutes before beginning to resolve. Hypotension was the adverse event designated as serious. This patient was HACA positive.

Infusion Reactions Resulting in Discontinuation of Study Treatment

In all rheumatoid arthritis Studies, 9 patients (1.6% of all infliximab-treated rheumatoid arthritis patients) were discontinued from study treatment because of an adverse event characterized as an infusion reaction. Three additional non-RA patients (1.4% of all infliximab-treated non-RA patients) were discontinued from study treatment (described under serious infusion reactions). None of the infusion reactions in the 9 RA patients was considered serious, and all were considered reasonably related to study medication. Two of these 9 patients were in the ATTRACT study, thus, of 342 infliximab-treated patients in ATTRACT, 0.58% had discontinuation of study treatment due to an infusion reaction.

- Patient T22-08005 (3 mg/kg q 8 wks) was a 45-year-old woman with a 1-year history of rheumatoid arthritis who experienced shortness of breath, a warm feeling on the left side of the face and neck, and low back pain approximately 50 minutes after the start of the week 6 infliximab infusion. The symptoms resolved within 2-7 minutes, no treatment was given and the infusion was not interrupted. However, the patient was discontinued from further study treatment for this infusion reaction which was considered mild and possibly related to study agent (HACA status not yet available).

- Patient T22-25004 (3 mg/kg q 4 wks) was a 60-year-old woman with a 15-year history of rheumatoid arthritis who experienced mild itching during the fourth infusion which lasted approximately 25 minutes and did not interrupt the infliximab infusion. Within 10 minutes of the start of the fifth infusion, the patient developed severe hives, the infusion was interrupted, and the hives resolved approximately 1 hour after the infusion was stopped. The patient was discontinued from further study treatment. (HACA status not yet available).

- Patient T07-01005 was a 28-year-old woman who received 2 infusions of 10 mg/kg infliximab followed by one 10 mg/kg infliximab infusion in extended treatment. Four minutes after the start of the third infusion, the patient became flushed, complained of a burning retrosternal sensation and lost consciousness. The infusion was discontinued. No pulse was detected. The patient recovered completely in 30 to 60 seconds with the administration of subcutaneous adrenaline. No additional infusions were given. Two weeks after this event, the patient had a HACA titer of 1:80.

- Patient T09-02012 was a 34-year-old woman who received 1 mg/kg infliximab followed by a 3 mg/kg infliximab infusion. The first infusion was uneventful. Thirteen minutes into the second infusion the patient complained of severe dyspnea, pressure in the head, nausea and vomiting. The infusion was stopped. Her vital signs were not significantly changed from baseline, no rashes were noted, and her lungs were clear. Oxygen was administered, and the patient felt well again 5 minutes after the infusion was discontinued. The infusion with study agent was not resumed. The patient was HACA negative.

- Patient T14-01018 was a 63-year-old woman who was randomized to receive MTX and 3 mg/kg of infliximab in each of 5 infusions. Ninety minutes into the third infusion, the patient developed an urticarial rash on the right arm, sternum and spine. The infusion was stopped approximately 30 minutes after the onset of the rash. She was treated with an oral antihistamine, and the urticaria vanished completely within 2.5 hours of stopping the infusion. The infusion was not resumed. The patient was pretreated with antihistamines before the fourth infusion, and a test dose of infliximab was administered. When no symptoms developed, the infusion was started. Forty minutes later, the patient developed pruritus of the limbs, and urticaria on the left arm, back, right thigh and the right shoulder. The infusion was interrupted and the patient received intramuscular antihistamines. The infusion was resumed slowly, and was completed within 3.5 hours of the start of the infusion. Her symptoms did not recur, and the urticaria had vanished by 3.75 hours after the end of the infusion. However, urticaria recurred 10 days after the fourth infusion accompanied by a petechial rash on both legs which disappeared without treatment within 6.5 weeks. Because of these events, the patient did not receive the fifth infusion of study medication. Four weeks after the fourth dose, the patient's HACA titer was 1:160.

- Patient T14-02003 was a 40-year-old woman who was randomized to receive 1 mg/kg infliximab without MTX in each of 5 infusions. Thirty minutes into the third infusion, the patient developed dyspnea, headache, facial erythema and a hive on her back. The infusion was interrupted and antihistamine treatment was given. The dyspnea resolved within 6 minutes and the headache within 25 minutes of onset. The erythema gradually decreased over the next 2 hours, and the hive resolved by 6 hours after onset. The infusion was continued slowly (beginning 50 minutes after interruption) and was completed 4.5 hours after the start of the infusion. There was no recurrence of symptoms during the infusion. Two and one-half hours after the end of the infusion, the patient again developed a headache, this time accompanied by a fever. The patient was medicated for pain, the both the fever and headache resolved within approximately 1 day. The patient did not receive any further infusions of study medication, and was withdrawn from the study. Four weeks after the third infusion this patient had a HACA titer of 1:40.

- Patient T14-02014 was a 39-year-old woman who was randomized to receive MTX plus 5 infusions of 1 mg/kg infliximab per infusion. The first 3 infusions were uneventful. Forty-five minutes into the fourth infusion the patient complained of mild chest tightness. The infusion was stopped immediately. The chest tightness lasted 5 minutes, disappeared without intervention, and the infusion was resumed. However, 45 minutes after reinitiation of the infusion the mild chest tightness appeared again, followed by chills 5 minutes later. The infusion was again interrupted, and symptoms resolved over a period of 60 minutes. The infusion was again resumed, this time at a very slow rate, and was completed with no other symptoms except mild chills. Before the fifth infusion, a test dose of infliximab was given. No reaction was noted. Forty-five minutes into the infusion the patient complained of mild chest tightness, chills and tingling in her fingers. The infusion was interrupted and the symptoms resolved spontaneously within 20 minutes. Symptoms recurred when the infusion was reinstituted and resolved spontaneously within 1 hour after stopping the infusion. The infusion was not reinitiated. Four weeks after the third infusion, the patient's HACA titer was 1:20.

- Patient T14-06001 was a 39-year-old woman who was randomized to receive 10 mg/kg infliximab without MTX in each of 5 infusions. She developed hypotension during each of the 3 infusions she received. At the end of the first infusion, she developed mild hypotension with chills. She was given intravenous saline, and the chills and hypotension resolved within 1.75 hours. Two and a half hours into the second infusion the patient once again became mildly hypotensive, and the infusion was

slowed. The hypotension resolved spontaneously within 2.75 hours after onset. Two and a half hours into the third infusion the patient became hypotensive again, and the infusion was stopped. No symptoms accompanied this episode. Additional fluid was administered, and the hypotension resolved after 65 minutes. The patient did not receive the rest of that infusion nor any subsequent infusions, and was withdrawn from the study. The patient was HACA negative.

- Patient T15/T17-02007 was a 48-year-old man with a 9-year history of rheumatoid arthritis who received 1 infusion of infliximab at a dose of 5 mg/kg as part of the T15 protocol followed by 3 doses of 10 mg/kg infliximab as part of the T17 trial. Fifteen to 30 minutes following the second infusion, the patient experienced diaphoresis, facial flushing, elevation of temperature, dizziness, transient amnesia, confusion and somnolence. During the events described above, the patient acted in a very uncharacteristic manner. He fell asleep rapidly and slept soundly for short periods of time and, when awake, appeared unsure of his surroundings. Approximately 2 hours after the end of the infusion, the patient was alert and oriented but stated that he could not recall any of the above events. The above events had resolved within 10 to 30 minutes and were not treated. All of the above events were considered not serious and possibly related to study drug. Approximately 40 minutes into the fourth infusion, the patient complained of dizziness and headache and became somewhat apathetic, amnesic, flushed and had involuntary hand movements. The infusion was stopped and all the above symptoms had resolved within 40 minutes with no treatment. The patient was discontinued from the study because of these events. The patient was HACA negative.

Infusion Reactions by HACA

Human antichimeric antibodies (HACA) have been observed in patients after infliximab administration. HACA assays may have interference from circulating infliximab for 4 to 12 weeks or more following infusion. Thus, HACA can only be excluded when the infliximab concentration is below the detectable level. For this reason, no HACA data are available yet for patients in T22 (ATTRACT). However, the results from T14 suggest that the presence of measurable concentrations of infliximab in samples collected 8 to 12 weeks following an infusion makes it unlikely that significant levels of neutralizing antibodies to infliximab are present. The relationship between the development of HACA and the occurrence of infusion reactions was examined to assess whether HACA could be correlated with infusion reactions. Table 5.3 presents the number of patients treated with infliximab in all studies with an infusion reaction by HACA status.

Included in the "HACA Negative At All Times" column are patients who were never HACA-positive and who could be evaluated for a minimum of 1 follow-up sample (and were HACA-negative). Excluded from the "HACA Negative At All Times" column are patients who, because of the persistence of infliximab in the serum, could not be evaluated for HACA. The "All Patients" column includes not only the "HACA Positive Anytime" and the "HACA Negative At All Times" patients but also includes the patients who could not be evaluated. HACA samples from studies T00 [redacted] T03 [redacted], and T12 [redacted] were not included in this analysis. Patients in all studies who were HACA-positive at any point during the trial were more likely than patients who were HACA-negative throughout the trial to experience a reaction to an infliximab infusion (36.3% vs 11.5%, respectively). More patients with dermatological and cardiopulmonary type of infusion reactions were also observed among the HACA-positive patients. Three of the 4 serious infusion reactions occurred in HACA-positive patients, and 6 of the 10 patients with reactions resulting in study treatment discontinuation were HACA-positive.

Table 5.3 Number of Infliximab-treated patients in all studies with an infusion reaction by development of HACA and by infusion reaction category per patient.

	HACA (+) at any time	HACA (-) at all times	All Patients[c]
Patients treated	80	209	412
Patients with ≥ 1 infusion reaction	28 (36.3%)	24 (11.5%)	77 (18.7%)
Pts with serious infusion reactions[a,b]	3 (3.8%)	1 (0.5%)	4 (1.0%)
Pts with reactions resulting in discontinuation[a]	6 (7.5%)	4 (1.9%)	10 (2.4%)

[a] For T22 (ATTRACT), no HACA data are available for week 30

[b] Denominator is patients treated

[c] Included are patients who were HACA(+) at any time, HACA(-) at all times, and those who were not evaluable for HACA at any time

5.2.5 Auto-immune syndromes

Although anti-TNF treatment with infliximab is associated with the development of anti-dsDNA antibodies, clinical manifestations in patients who developed these antibodies have been infrequent. Three of 771 patients treated with infliximab developed clinical signs of lupus, 2 of them reported as part of the Crohn's disease license application.

- Patient T14-01009 was a 36-year-old woman who had a 6-year history of rheumatoid arthritis. As part of the trial, she received a series of 5 cA2 treatments (3 mg/kg cA2) in combination with methotrexate. Prior to the last infusion, the patient was noted to be short of breath which was believed to be secondary to bronchitis. Her symptoms responded to antibiotics, and the 14-week infusion was administered. Three weeks after the infusion she developed active arthritis, dyspnea, pleuritic chest pain and low grade fever. In addition, she had anterior chest pain, and pericarditis was diagnosed by electrocardiogram (ECG). A diagnosis of systemic lupus erythematosus was made based on the clinical findings and her serologic profiles. The patient developed ANA at week 6 and showed evidence of anti-dsDNA antibodies at the same timepoint. Sera from later timepoints not required by the protocol were analyzed. She was treated with oral corticosteroids and her symptoms resolved within 6 to 8 weeks of initiation of treatment. There was no report of renal or central nervous system involvement. Approximately 3.5 months after the last infusion of cA2, her serologic profile normalized.

- Patient T16-08004 was a 25-year-old woman with a 13-year history of Crohn's disease who was receiving concomitant therapy with mesalamine. She received 20 mg/kg of infliximab as her initial infusion, followed by an open-label 10 mg/kg dose approximately 7 weeks later. Approximately 1½ months after a third infusion of 10 mg/kg (26 weeks after the initial infusion), the patient began complaining of joint pain and swelling in her ankles, feet, toes, wrists, knees and shoulders. Her ANA had been negative at entrance to the study but was positive at 1:320 at 12 weeks, and 1:640 at 20 weeks with negative anti-dsDNA at the central laboratory. The ANA determined at the local laboratory (with no baseline value obtained) was positive at a titer of 1:2560 with an anti-dsDNA level of 40 IU/mL (normal 0-24 IU/mL). The patient was diagnosed with drug-induced lupus. She was started on prednisone 20 mg daily and the patient's symptoms had resolved within 6 months following the last infusion.

- Patient T22-18005 was a 48-year-old female with an 18-year history of rheumatoid arthritis treated with MTX, and was randomized to receive infliximab 10 mg/kg q 8 wks. Approximately 2 weeks after receiving the second (week 2) infusion, the patient developed a persistent rash on the hands and forearms, and a biopsy showed mild perivascular inflammatory infiltrate suggestive of drug reaction and study treatment was discontinued at that time. The patient did not receive any additional study agent infusions beyond week 2 due to the rash. An immunology screen performed approximately 2 months later was ANA-negative, showed low complement (C4), and was positive for cardiolipin

antibodies. The rash on hands and forearms resolved approximately 3 months after onset. One month later, the patient developed itchy spots on forearms, erythema on both cheeks, and puffiness around eyes, and a second immunology screen showed anticardiolipin antibodies, low C4, weakly positive ANA, and negative anti-dsDNA. A diagnosis of drug-induced lupus erythematosus was made based upon the results of this immunology screen, as well as a butterfly pattern facial skin rash in combination with the rash on forearms. The erythema was considered ongoing beyond week 30.

5.3 Review of Safety Data from T24 (Delayed Hypersensitivity Reactions)

This section reviews the open label clinical trial, T24. This trial was a multicenter, phase 4 clinical trial in patients with Crohn's disease who had received prior infliximab treatment in earlier studies (T11, T16, and T20) and who were seeking retreatment. The study began on June 25, 1998 and was terminated on December 7, 1998. In this study, up to 5 doses of 5 mg/kg of infliximab were to be administered every 4 weeks, and/or as needed. A total of 40 patients were enrolled.

Ten of the 40 patients experienced delayed hypersensitivity type (DHT) reactions 3 to 12 days after retreatment with infliximab. Six of these reactions were considered serious. These events occurred upon retreatment anywhere from 2 to 4 years following their prior infliximab administration. These patients and events are summarized in Appendix 5.A. The lots given to these patients in the earlier trials were [redacted], and [redacted] (lyophilized formulation). Only one of the ten patients who experienced a delayed hypersensitivity reaction had received the lyophilized formulation. In addition to the patients enrolled into T24, the sponsor received reports of delayed hypersensitivity reactions in two additional patients who had received lot [redacted] in T16. The sponsor submitted data regarding the formulations to [redacted]. The product reviewer, Kurt Brorson, concluded that there were insufficient data to correlate the development of a secondary immune response to the prior formulation.

Clinically, lyophilized product was introduced for use in T20 where 63 patients received infliximab. Among the earlier trials, 104 patients received a [redacted] The breakdown of patients with and without delayed hypersensitivity reactions in T24 by there prior study participation is shown in Table 5.4. There were 4 patients who had participated in T11 and all developed a delay hypersensitivity-type reaction. The number of patients enrolled into T22 and who had participated in either T16 or T20 were comparable (19 and 17, respectively) and there is a higher incidence of delayed hypersensitivity reactions in patients who were enrolled in either T11 or T16 compared to T20.

Table 5.4 Distribution of delayed hypersensitivity type (DHT) reaction in patient enrolled in T24 by their prior clinical trial exposure.

Prior clinical trial	Total number in T24	Pts with DHT	Pts without DHT
T11	4	4	0
T16	19	5	14
T20	17	1	16
Total	40	10	30

HACA was measured after infusion of infliximab in the majority of patients in T24 who did not develop a delayed hypersensitivity type reaction (Table 5.5). There were 4 patients who had participated in T16 and 3 patients from T20 who developed HACA after re-exposure to infliximab in T24 but who did not experience a delayed hypersensitivity reaction. The HACA levels are relatively low with the exception of the 1:5,120 HACA titre in a patient who had participated in T20 (lyophilized formulation). Because T24 was terminated early, it remains unknown whether or not these patients would have developed DHT reactions associated with higher levels of HACA with additional exposure to infliximab. However, the presence of low level HACA development in patients who had been enrolled in T20 suggests that there remains a risk for DHT reactions in patients who had received prior lyophilized formulation.

Table 5.5 HACA response in patients enrolled in T24 who did not experience a delayed hypersensitivity type (DHT) reaction.

Prior study	Patients without a DHT reaction			
	Total	HACA positive	HACA negative	No HACA sample
T11	0			
T16	14	1:80 at week 4 after infusion 1 1:10 at week 4 after infusion 2 1:80 at week 4 after infusion 2 1:640 at week 4 after infusion 1	8	2
T20	16	1:40 at week 4 after infusion 1 1:160 after week 4 after infusion 1 1:5,120 at week 4 after infusion 1	7	6

Independent of the differences formulation and particulate matter (which would be filtered), a major possibility for the development of delayed hypersensitivity reactions to consider is differences in the amount of [redacted]

5.4 Summary:

The development of a delayed hypersensitivity type reaction in patients who are re-exposed to infliximab after an interval of time appears to be related to development of an antibody response to infliximab. We cannot conclude with the data available that there is a direct correlation between the risk of development of DHT reaction with the type of formulation, i.e., [redacted] or lyophilized. Although the incidence may be lower in patients who received prior lyophilized formulation, it did occur in one subject and a range of HACA response was seen in 3 subjects from T20. The fact that the highest HACA level (1:5,120) occurred for patients with HACA response without systemic reaction is noteworthy. If the immune reaction is associated with the presence of bovine IgG, then patients currently receiving commercial product are at risk for DHT reaction since its bovine IgG levels are [redacted]

Appendix 5.A. Summary of patients in T24 who experienced delayed hypersensitivity reactions

Patient (Age, Sex)	Previous Trial	Previous Dose (lot)	T24 dose (lot); time since prior dose	Adverse event reported (onset, days post infusion)	HACA titer
02015 (24, F)	T16	20 mg/kg [redacted]	5 mg/kg x2 [redacted] 2Y11M	Myalgia, sore throat, fever, chills, flu sx (10 days p 1st infusion); polyarthropathy (12 days p 2nd infusion)	[redacted]
03003 (40, M)	T11	10 mg/kg x1 [redacted]	5 mg/kg x1 [redacted] 3Y10M	Asymmetrical shoulder & hip arthralgia, fever, TMJ arthralgia, leg stiffness (8d)	[redacted]
03004 (51, F)	T20	5 mg/kg x3 [redacted]	5 mg/kg x1 [redacted] 2Y2M	Edema of lips, hands, eyes, pruritus, rash, fever, urticaria, dysphagia, myalgia (7d)	[redacted]
03006 (41, M)	T11	5 mg/kg x1 [redacted]	5 mg/kg x1 [redacted] 3Y11M	Asymmetrical TMJ and polyarticular arthralgia, fever, rash no objective arthritis (7d)	[redacted]
03009 (48, F)	T16	20 mg/kg x1 10 mg/kg x4 [redacted]	5 mg/kg x1 [redacted] 2Y6M	Chills, asymmetrical polyarthralgia, TMJ stiffness, fever, no objective arthritis (9d)	[redacted]
05006 (42, M)	T11	5 mg/kg x1 [redacted]	5 mg/kg x2 [redacted] 3Y11M	Polyarthralgia, myalgia (7d)	[redacted]
22001 (39, M)	T11	10 mg/kg x1 [redacted]	5 mg/kg x1 [redacted] 4Y	TMJ arthralgia, myalgia, fever, rash, sore throat (8d)	[redacted]
22002 (45, F)	T16	20 mg/kg x1 10 mg/kg x4 [redacted]	5 mg/kg x1 [redacted] 2Y6M	Pruritus, rash, HA, myalgia (7d)	[redacted]
22003 (31, F)	T16	5 mg/kg x1 10 mg/kg x4 [redacted]	5 mg/kg x1 [redacted] 2Y6M	Diffuse skin rash, myalgia, arthralgia (10d)	[redacted]
22004 (38, F)	T16	20 mg/kg x1 10 mg/kg x4 [redacted]	5 mg/kg x1 [redacted] 2Y4M	Diffuse rash (3d)	[redacted]

6.0 Conclusions regarding Overall Safety and Efficacy of Infliximab

Results from the pivotal trial, T22 (ATTRACT) indicate that all of the doses and dose regimens of infliximab evaluated in patients with rheumatoid arthritis who are being treated with MTX show clinical benefit. Review of these data for adverse events, indicate that patients treated with infliximab have an increased risk for infection and infusion reactions. Patients with rheumatoid arthritis who receive MTX may have a slightly increased risk of experiencing adverse events known to occur with MTX, e.g., increased liver enzymes, ulcerative stomatitis. In controlled clinical trials, only 555 patients with rheumatoid arthritis have been exposed to infliximab, so the degree of these safety concerns cannot be accurately assessed. In addition, it cannot be determined from the small exposure history if patients being treated with both infliximab and MTX will be at increased risk for the more serious but less common adverse events known to occur with MTX treatment, e.g., puhnonary fibrosis.

There remain some important safety questions that cannot be answered with this small overall database: Are patients treated with infliximab at greater risk for pancreatitis and biliary tract disease (acalculous cholecystitis was seen in both T22 and in T20, the occurrence of pancreatitis was higher in patients enrolled in T22 treated with inflixirnab)?

As shown by review of the data generated in the phase study, T14, higher serum levels of infliximab were maintained and more patients experienced benefit when infliximab was given in conjunction with MTX. The most likely explanation for this interaction, is that MTX decreases a neutralizing immunological response to infliximab. Based upon these results, the sponsor evaluated infliximab in conjunction with MTX in patients with rheumatoid arthritis. Consequently, infliximab should be licensed to be given in conjunction with MTX.

The clinical implications of the immunogenicity of infliximab remains poorly defmed. The following lists want is known from the clinical data:

- It is known that an immunological response to infliximab can neutralize the product both pharmacokinetically and clinically, is assocated with both acute and delayed hypersensitivity reactions, and most likely explains the infusion reactions.
- It appears that infliximab depresses the immunological response since benefit was seen in patients treated with higher doses of infliximab without MTX in T14..
- There may be a difference in the degree of immunogenicity between the product studied in earlier trials (i.e., T14 and T16) and that studied in later clinical trials (e.g., T22 and T20) as shown by the difference in the incidence of delayed hypersensitivity reactions seen in patients in T24. However, the current product has been associated with delayed hypersensitivity reactions, so the immunological stimulant is still present.
- It appears from review of infusion reactions in all of the clinical trials that co-administration of an immunosuppressant diminishes the risk for an infusion reaction.

In summary, I recommend that infliximab be licensed for the treatment of patients with rheumatoid arthritis who have not responded to treatment with MTX. Infliximab should be administered with MTX. The sponsor should continue to investigate the clinical significance of the immune reactions to infliximab in order to determine whether or not patients who are not receiving MTX will experience clinical benefit. Physicians and patients should be alerted that the safety database is extremely small and should be encouraged to report adverse events, particularly, infections, liver/biliary disease, and malignancies.